Original Article

Effect of human epidermal growth factor receptor 2 overexpression in metastatic colorectal cancer on standard chemotherapy outcomes

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Background: In metastatic colorectal cancer (mCRC), the prognostic relevance of the human epidermal growth factor receptor-2 (HER2) remains controversial. We evaluated the impact of HER2 overexpression on outcomes of standard chemotherapy in patients with mCRC.

Methods: This retrospective study included patients with mCRC who received standard chemotherapy for mCRC and were tested for HER2 expression at Samsung Medical Center, Seoul, Korea, between January 15, 2017, and February 05, 2022. The HER2 test was performed using immunohistochemistry. We assessed the objective response rate (ORR), overall survival (OS), and progression-free survival (PFS) according to HER2 status. All statistical analyses were performed using SPSS® version 25 (IBM, Armonk, NY, USA).

Results: In total, 108 patients were included; 10 (9.3%) had HER2-positive tumors. The ORR for patients with mCRC receiving standard chemotherapy did not differ for HER2-positive and HER2-negative tumors. The median PFS for patients with mCRC with HER2-positive or HER2-negative tumors after receiving first-line chemotherapy was 18.52 months [95% confidence interval (CI): 4.355–32.695] or 10.95 months (95% CI: 9.317–12.585; P=0.417), respectively, and that after second-line chemotherapy was 7.08 months (95% CI: 6.801–7.363) or 5.34 months (95% CI: 4.433–6.255; P=0.837), respectively. Likewise, OS did not differ according to HER2 expression (median OS: HER2-positive tumors, 49.1 months (95% CI: 0.000–98.365); HER2-negative tumors, 37.7 months (95% CI: 27.111–48.366; P=0.410).

Conclusions: The tumor response and survival of patients with mCRC after standard chemotherapy did not differ by HER2 expression. These findings suggest that the status of HER2 expression need not be considered when choosing regimens as the current first- and second-line treatments.

Keywords: Colorectal cancer (CRC); human epidermal growth factor receptor 2 (HER2); *c-erbB-2* gene

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Introduction

Background

Colorectal cancer (CRC) is the third most frequently diagnosed cancer worldwide. It is the second leading cause of cancer death, accounting for 10% of the total (1). Approximately 20% of patients are initially diagnosed with metastatic CRC (mCRC), while around 70% of patients with early-stage disease progress to metastatic disease (2,3). The use of chemotherapy with additional targeted therapies, including anti-epidermal growth factor receptor (EGFR) antibody (cetuximab or panitumumab) or anti-vascular endothelial growth factor (VEGF) antibody (bevacizumab), has improved the overall survival (OS) of patients with mCRC by approximately 25–35 months (4-11).

The human epidermal growth factor receptor-2 (HER2; also known as the c-erbB-2 protein) is encoded by the *ERBB2* gene located on chromosome 17q21. The HER2 protein acts as a receptor tyrosine kinase and activates the phosphatidylinositol 3-kinase (PI3K/AKT) and RAS/RAF/MEK/ERK pathways. Therefore, *ERBB2* genes and the HER2 protein regulate cell proliferation and survival (12). Dysregulated overexpression or amplification of HER2 drives oncogenesis (13), occurring in about 20% of invasive breast cancer (14), about 20% of gastric cancer (15), and about 1–30% of lung (16). The presence of HER2 overexpression/amplification is associated with a worse prognosis than HER2-negative cancer. It has become clinically valuable as a predictive marker of response to specific treatments; the HER2 protein is also a treatment target (14-17).

Highlight box

Key findings

- The tumor response and survival of patients with metastatic colorectal cancer (mCRC) after standard chemotherapy did not differ by the HER2 expression.

What is known and what is new?

- In mCRC, the prognostic relevance of the HER2 remains controversial.
- The tumor response, progression-free survival, and overall survival among patients with mCRC who underwent first- and second-line chemotherapy did not significantly differ according to HER2 expression.

What is the implication, and what should change now?

- The status of HER2 expression need not be considered when choosing regimens as the current first- and second-line treatments.

Rationale and knowledge gap

In mCRC, the prevalence of HER2 overexpression or amplification reported in various studies ranges from about 1.0% to 14.0% (18-21). Several studies have investigated the role of HER2 overexpression or amplification in mCRC: some have reported that *HER2* gene amplification was associated with liver metastases (22), lung metastases (23), or central nervous system metastases (24). However, the prognostic relevance of HER2 in mCRC remains controversial, in contrast to that in breast cancer. In CRC, overexpression or amplification of HER2 is a predictive biomarker of resistance to anti-EGFR therapy (23,25) and an independent prognostic factor (22,26). However, other studies have reported no association between HER2 expression and prognosis (19,27). Moreover, all of the HER2 dual blockade treatment, trastuzumab-lapatinib (HERACLES trial), trastuzumab-pertuzumab (MYPATHWAY trial), and trastuzumab deruxtecan (DESTINY-CRC01 trial), have proven effective as third-line and beyond. The first- and second-line treatment standard for mCRC remains the combination of anti-EGFR/anti-VEGF and 5-fluorouracil backbone chemotherapy, regardless of HER2 overexpression (3,28-30).

Objective

In this study, we aimed to evaluate the impact of HER2 overexpression on treatment outcomes when employing standard first- and second-line chemotherapy and to analyze the prognostic utility of HER2 overexpression in patients with mCRC. We present this article in accordance with the REMARK reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-375/rc).

Methods

Patients

This retrospective study included patients with mCRC who received standard first- and second-line chemotherapy at Samsung Medical Center, Seoul, Korea, between January 15, 2017, and February 5, 2022. Simultaneously, the patients were available for the c-erbB-2 immunohistochemistry (IHC) test. Clinical data, including physical examinations, pathology reports, imaging, laboratory data, and demographic information, were collected from the patients' electronic medical records. History of prior surgical, adjuvant, or palliative treatment, toxicity profile, treatment

response, and survival data were documented. The last survival and treatment response data collection date was September 13, 2022. This study was approved by the Institutional Review Board (IRB) of the Samsung Medical Center in Seoul (IRB No. 2022-12-067), and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). As this study was performed retrospectively based on existing medical records, the requirement for written consent from the patients was waived by the IRB.

HER-2 (c-erbB-2) immunohistochemistry test

The IHC HER2 test was performed using a VENTANA anti-HER2/neu rabbit monoclonal primary antibody (clone 4B5, Ventana Medical System; Roche, Tucson, AZ, USA) at the Department of Pathology, Samsung Medical Center, Seoul. The results of the HER2 IHC assay were interpreted according to the HERACLES Diagnostic Criteria (31). An HER2 positive tumor was defined as an IHC intensity score of 3+ in >50% of the tumor cells, an IHC intensity score of 3+ in 10–50% of the tumor cell and fluorescence in situ hybridization (FISH) positivity, or an IHC intensity score of 2+ in >50% of the tumor cells and FISH positivity. FISH positivity was defined as an HER2:CEP17 ratio higher than two in >50% of the tumor cells.

Outcomes and statistical analyses

Response to treatment was assessed by physicians according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The ORR was defined as the percentage of patients with a complete response (CR) or partial response (PR). Meanwhile, the disease control rate (DCR) was defined as the percentage of patients with CR, PR, or stable disease (SD). The PFS was defined as the duration from initiating the first treatment cycle to disease progression or any cause of death. The OS was defined as the duration from initiating the first treatment cycle to any cause of death. Categorical variables were compared using Fisher's exact test. Using Cox regression, we conducted univariate and multivariate analyses to assess prognostic factors. We estimated all univariate models and included independent variables with P<0.1 in the multivariate model. Also, clinically significant variables were included using background knowledge. We estimated PFS and OS using Kaplan-Meier curve analyses. We performed the log-rank test to assess survival differences according to HER2 status. A P value <0.05 was considered to reflect statistical significance. All statistical analyses were performed using SPSS® version 25 (IBM, Armonk, NY, USA).

Results

Patient characteristics

A total of 111 patients diagnosed with mCRC and available for the HER2 IHC test between January 15, 2017, and February 05, 2022, were included in the analysis (*Figure 1*). Among them, 6 patients were excluded for lack of data on chemotherapies and tumor response; 1 was HER2-positive, and 5 were HER2-negative. Patient characteristics are presented in *Table 1*. The median age was 58 years (21–84 years), and 65 (61.9%) patients were male. Microsatellite instability (MSI-high) was detected in 4 (3.8%) patients. The median total tumor mutational burden (TMB) was 6.3 mutations per Megabase (mt/Mb) in all patients, and 22 (21.0%) patients were classified into the TMB-high group (≥10 mt/Mb). Almost all patients received FOLFIRI (5-fluorouracil, leucovorin, and irinotecan) and FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) as first- and second-line chemotherapy, respectively.

In addition, as first- and second-line chemotherapy, 85.7% and 44.8% of patients received bevacizumab, while 8.6% and 1.0% received cetuximab, respectively. Among the 105 patients, 9 (9%) had HER2-positive tumors. Tumor-sidedness was not significantly different between the HER2-positive and HER2-negative groups. The primary tumor site was more often in the colon in the HER2-positive group (88.9%, 8/9) than in the HER2-negative group (65.6%, 63/96), but this was not statistically significant. Furthermore, the distributions of *KRAS*, *NRAS*, and *BRAF* mutations did not differ regarding HER2 status.

Efficacy of chemotherapy according to HER2 expression

We compared the efficacy of first- or second-line chemotherapy concerning HER2 overexpression. For patients who underwent first-line chemotherapy (*Table 2*), the ORR and DCR were 43.8% [46/105, 95% confidence interval (CI): 34.1–53.8%] and 92.4% (97/105, 95% CI: 85.5–96.7%), respectively. Among the 9 patients with HER2-positive tumors, 3 (11.1%) achieved CR, 2 achieved PR, and 2 maintained SD, resulting in an ORR of 55.6% (5/9, 95% CI: 21.2–86.3%) and a DCR of 77.8% (7/9,

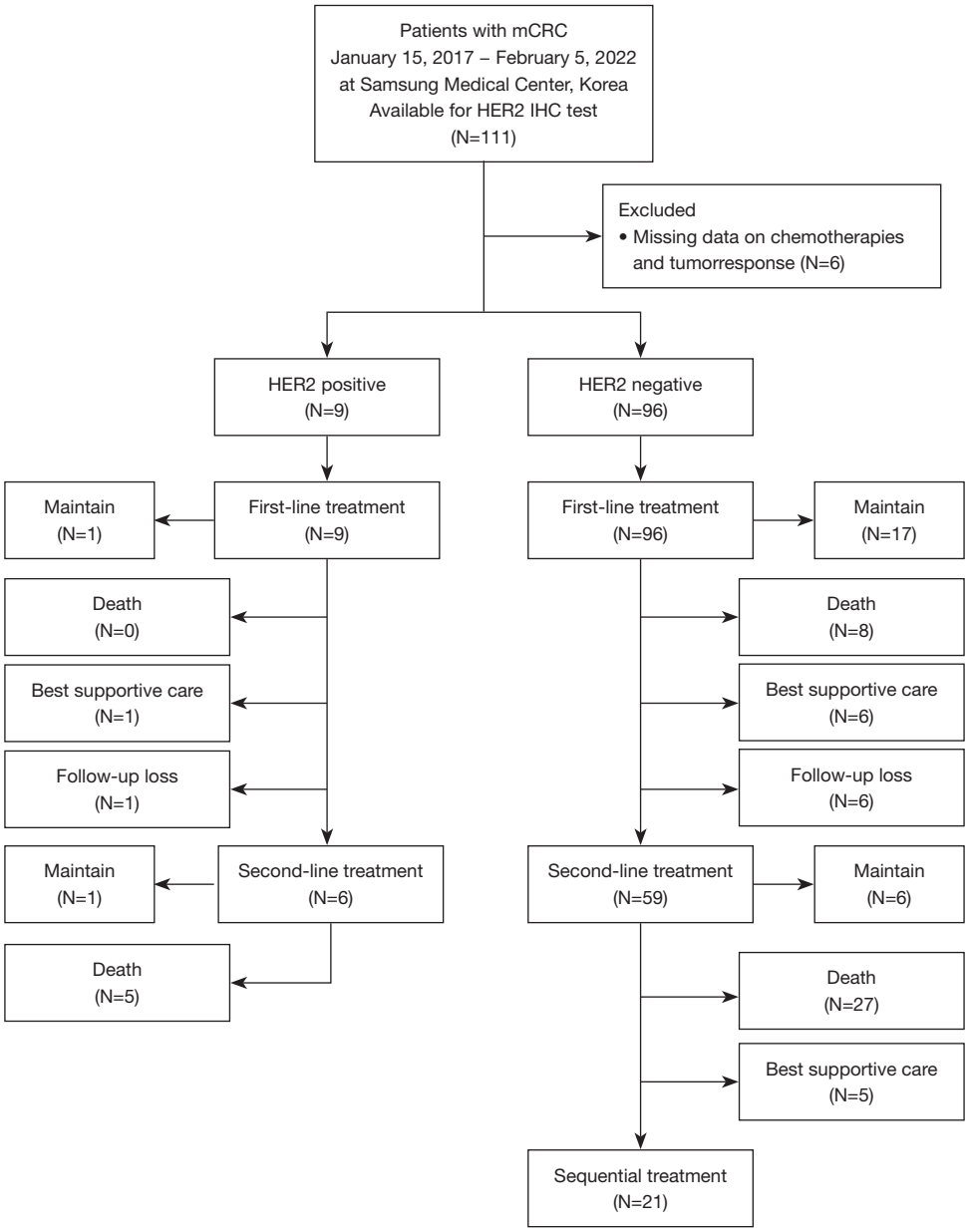

Figure 1 The flow chart of patients. mCRC, metastatic colorectal cancer; HER2, human epidermal growth factor receptor-2.

95% CI: 40.0–97.2%). Among patients with mCRC who underwent first-line chemotherapy, the ORR (P=0.501) and DCR (P=0.140) did not differ between HER2-positive or HER2-negative tumors. Concerning second-line chemotherapy, there were no significant differences in ORR (P=1.000) and DCR (P=1.000) in mCRC patients with HER2-positive and negative tumors (*Table 3*).

Predictive and prognostic analysis according to HER2 expression and other variables

Among patients who underwent first-line chemotherapy, the median PFS was 11.05 months (95% CI: 9.416–12.682), and there was no difference in PFS to first-line chemotherapy between HER2-positive and -negative tumors (P=0.431, *Figure 2A*). The median PFS to second-

Table 1 Baseline characteristics of all enrolled patients and HER2-negative and -positive metastatic colorectal cancer patients

Characteristics	No. of patients (N=105, 100%)	HER2-negative (N=96, 91%)	HER2-positive (N=9, 9%)	P
Age (years)	58 [21–84]	58 [21–84]	59 [34–67]	0.483
Sex				
Male	65 (61.9)	59 (61.5)	6 (66.7)	1.000
Female	40 (38.1)	37 (38.5)	3 (33.3)	
ECOG				
0–1	96 (91.4)	87 (90.6)	9 (100.0)	1.000
≥2	9 (8.6)	9 (9.4)	0	
Primary site of disease				
Colon	71 (67.6)	63 (65.6)	8 (88.9)	0.266
Rectum	34 (32.4)	33 (34.4)	1 (11.1)	
Tumor sidedness				
Right	23 (21.9)	20 (20.8)	3 (33.3)	0.407
Left[†]	82 (78.1)	76 (79.2)	6 (66.7)	
KRAS mutation[‡]				
No	59 (56.2)	53 (55.2)	6 (66.7)	0.728
Yes	46 (43.8)	43 (44.8)	3 (33.3)	
NRAS mutation[‡]				
No	103 (98.1)	94 (97.9)	9 (100.0)	1.000
Yes	2 (1.9)	2 (2.1)	0	
BRAF mutation[‡]				
No	97 (92.4)	89 (92.7)	8 (88.9)	0.524
Yes	8 (7.6)	7 (7.3)	1 (11.1)	
MMR status[‡]				
MSS	101 (96.2)	92 (95.8)	9 (100.0)	1.000
MSI-high	4 (3.8)	4 (4.2)	0	
TMB[‡] (mt/mb)	6.30 [0–125]	6.3 [0–125]	7.00 [2.3–10.2]	
TMB-low	83 (79.0)	75 (78.1)	8 (88.9)	0.681
TMB-high	22 (21.0)	21 (21.9)	1 (11.1)	
Biological targeted agents				
Antiangiogenic inhibitors containing	99 (94.3)	90 (93.8)	9 (100.0)	1.000
Anti-EGFR inhibitor containing	9 (8.6)	8 (8.3)	1 (11.1)	0.569

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	No. of patients (N=105, 100%)	HER2-negative (N=96, 91%)	HER2-positive (N=9, 9%)	P
First-line chemotherapy regimen				
Bevacizumab + FOLFIRI	27 (25.7)	25 (26.0)	2 (22.2)	
Bevacizumab + FOLFOX	63 (60.0)	57 (59.4)	6 (66.7)	
Cetuximab + FOLFIRI	9 (8.6)	8 (8.3)	1 (11.1)	
Cetuximab + FOLFOX	0	0	0	
Other‡	6 (5.4)	6 (6.3)	0	
Second-line chemotherapy regimen	(n=64)	(n=58)	(n=6)	
Bevacizumab + FOLFIRI	28 (43.8)	24 (41.4)	4 (66.7)	
Bevacizumab + FOLFOX	19 (29.7)	17 (29.3)	2 (33.3)	
Cetuximab + FOLFIRI	1 (1.6)	1 (1.7)	0	
Cetuximab + FOLFOX	0	0	0	
Aflibercept + FOLFIRI	10 (15.6)	10 (17.2)	0	
Aflibercept + FOLFOX	1 (1.6)	1 (1.7)	0	
Other§	5 (7.8)	5 (8.6)	0	

Data are presented as n (%) or median [range]. †, tumors located at the descending colon, sigmoid colon, and rectum were defined as left-sided colorectal cancer. ‡, KRAS, NRAS, and BRAF mutation, MMR status, and TMB were tested using next-generation sequencing. The cut-off value for TMB-high was 10 mutations/megabase. §, other chemotherapies included capecitabine, XELOX (capecitabine, leucovorin, and oxaliplatin), or FOLFIRI or FOLFOX without target agents. BRAF, B-Raf Proto-Oncogene; ECOG, European Cooperative Oncology Group score; FOLFIRI, 5-fluoruracil, leucovorin, and irinotecan; FOLFOX, 5-fluoruracil, leucovorin, and oxaliplatin; HER2, human epidermal growth factor receptor-2; KRAS, Kirsten ras oncogene homolog; MMR, mismatch repair; MSI, microsatellite instability; MSS, microsatellite stable; NRAS, neuroblastoma RAS viral oncogene homolog; TMB, tumor mutational burden.

Table 2 Response to first-line chemotherapy according to HER2 expression

Best response to first line	Total patients (N=105)	HER2 negative (N=96)	HER2 positive (N=9)	P
Objective response rate (%, 95% CI†)	43.8 (34.1, 53.8)	42.7 (32.7, 53.2)	55.6 (21.2, 86.3)	0.501
Disease control rate (%, 95% CI†)	92.4 (85.5, 96.7)	93.8 (86.9, 97.7)	77.8 (40.0, 97.2)	0.140
Complete response	4 (3.8)	1 (1.0)	3 (33.3)	
Partial response	42 (40.0)	40 (41.7)	2 (22.2)	
Stable disease	51 (48.6)	49 (51.0)	2 (22.2)	
Progressive disease	8 (7.6)	6 (6.3)	2 (22.2)	

Objective response rate and disease control rate were compared using Fisher's exact test. †, The 95% confident interval was calculated using the Clopper-Pearson method. HER2, human epidermal growth factor receptor-2; CI, confident interval.

line chemotherapy was also not different between HER2-positive and -negative tumors (P=0.861; *Figure 2B*). The median OS of the 105 patients was 37.74 months (95% CI: 26.562–49.914). Like PFS, the median OS was longer in the HER2-positive group, but this lacked statistical significance (P=0.245, *Figure 3*).

The results of the prognostic analysis of PFS and OS to first-line therapy are provided in *Tables 4,5*. When HER2 overexpression was assessed as a prognostic marker, there was no evidence as an independent factor for PFS to first-

Table 3 Response to second-line chemotherapy according to HER2 expression

Best response to second line	Total patients (N=64)	HER2 negative (N=59)	HER2 positive (N=5)	P
Objective response rate (%, 95% CI[†])	18.8 (10.1, 30.5)	18.6 (9.7, 30.9)	20.0 (0.5, 71.6)	1.000
Disease control rate (%, 95% CI[†])	79.7 (67.8, 88.7)	79.7 (67.2, 89.0)	80.0 (28.4, 99.5)	1.000
Complete response	0	0	0	
Partial response	12 (18.8)	11 (18.6)	1 (20.0)	
Stable disease	39 (60.9)	36 (61.0)	3 (60.0)	
Progressive disease	13 (20.3)	12 (20.3)	1 (20.0)	

Objective response rate and disease control rate were compared using Fisher's exact test. [†], The 95% confidential interval was calculated using the Clopper-Pearson method. HER2, human epidermal growth factor receptor-2; CI, confident interval.

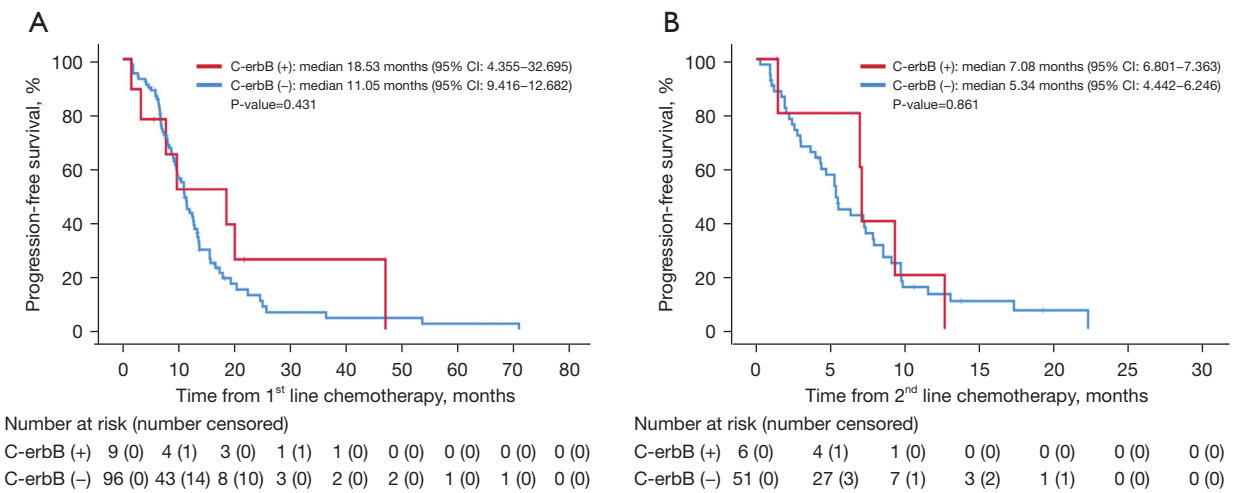

Figure 2 Kaplan-Meier estimates of progression-free survival. The median follow-up duration was 22.6 months (range, 1.93–92.17). There was no statistically significant difference in PFS for first- and second-line chemotherapy, respectively, between HER2-positive and HER2-negative mCRC. (A) PFS for first-line chemotherapy. Median PFS was 18.53 months (95% CI: 4.355–32.695) for HER2-positive and 11.05 months (95% CI: 9.416–12.682, P=0.431) for HER2-negative mCRC. (B) PFS for second-line chemotherapy. Median PFS was 7.08 months (95% CI: 6.801–7.363) for HER2-positive and 5.34 months (95% CI: 4.442–6.246, P=0.861) for HER2-negative mCRC. HER2, human epidermal growth factor receptor-2; CI, confident interval; PFS, progression-free survival; mCRC, metastatic colorectal cancer.

line chemotherapy in multivariate analysis [hazard ratio (HR), 0.82; 95% CI: 0.35–1.94, P=0.652]. *BRAF* mutation and MSI-high were significant risk factors for the PFS to first-line treatment in univariate and multivariate analyses. The HR of *BRAF* mutation was 2.49 (95% CI: 1.04–5.96, P=0.041), and the HR of MSI-high was 3.83 (95% CI: 1.24–11.8, P=0.019), in multivariate analysis (*Table 4*). Similarly, there was no evidence that HER2 overexpression was an independent prognostic factor for OS in the multivariate analysis (HR, 1.50; 95% CI: 0.57–3.90; P=0.411). *ECOG* and *BRAF* mutation were statistically significant, with HRs 6.05 (95% CI: 1.98–18.5, P=0.002) and 3.06 (95% CI: 1.03–9.06, P=0.043, *Table 5*), respectively.

Discussion

Key findings

The present study evaluated the impact of HER2 overexpression on the outcomes of patients with mCRC who underwent standard first- and second-line chemotherapy and analyzed the prognostic role of HER2

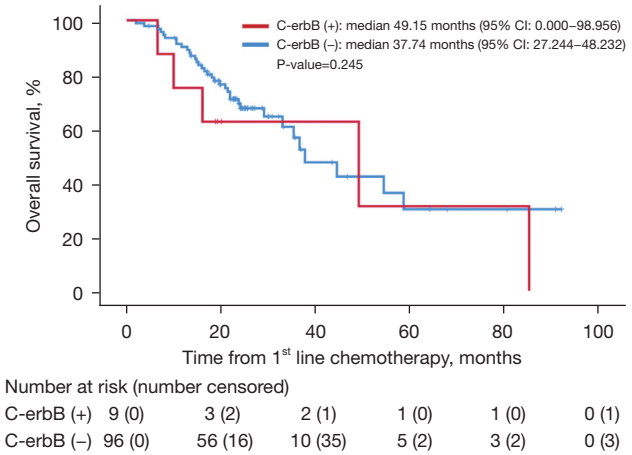

Figure 3 Kaplan-Meier estimates of overall survival. There was no difference in overall survival between HER2-positive and HER2-negative mCRC. Median overall survival was 49.15 months (95% CI: 0.000–98.956) *vs.* 37.74 months (95% CI: 27.244–48.232, P=0.245). HER2, human epidermal growth factor receptor-2; CI, confident interval; mCRC, metastatic colorectal cancer.

overexpression. The tumor response, PFS, and OS among patients with mCRC who underwent first- and second-line chemotherapy did not significantly differ according to HER2 expression. Therefore, HER2 overexpression was not predictive of the response rate for first- and second-line chemotherapy in patients with mCRC. Furthermore, HER2 overexpression was not a prognostic factor for OS. These findings suggest that HER2 expression need not be considered when choosing first- or second-line treatment regimens. However, these findings must be interpreted with caution as the study patients did not receive anti-HER2 directed therapy, a useful treatment option for HER2-positive mCRC.

The reported prevalence of HER2 overexpression or amplification in various studies has ranged from 1.0% to 14.0% (18-22,25-27). In the present study, 9% of patients with mCRC had HER2-positive tumors, toward the higher end of incidences reported in previous studies. The definition of HER2 positivity in CRC has not been

Table 4 Univariate and multivariate cox regression analyses of clinicopathological factors for the progression-free survival to 1st line chemotherapy

Variables	No. of patients (n=105)	No. of events (n=79)	Univariate		Multivariate	
			HR (95% CI)	P	HR (95% CI)	P
Age			0.99 (0.97, 1.01)	0.195	0.99 (0.97, 1.01)	0.407
Sex			1.20 (0.76, 1.90)	0.438	1.20 (0.73, 1.96)	0.480
Male	65	49				
Female	40	30				
ECOG			1.32 (0.61, 2.89)	0.481	1.57 (0.66, 3.76)	0.311
0–1	96	72				
≥2	9	7				
Location			1.08 (0.67, 1.75)	0.739	0.99 (0.58, 1.69)	0.965
Colon	71	54				
Rectum	34	25				
Sidedness						
Right	23	15	1.08 (0.61, 1.90)	0.793	1.06 (0.54, 2.07)	0.860
Left†	82	64				
Differentiation	(n=83)	(n=66)				
Well	8	4	Reference			
Moderate	66	53	0.96 (0.35, 2.69)	0.944		
Poor	9	9	0.76 (0.22, 2.60)	0.658		

Table 4 (*continued*)

Table 4 (*continued*)

Variables	No. of patients (n=105)	No. of events (n=79)	Univariate		Multivariate	
			HR (95% CI)	P	HR (95% CI)	P
KRAS‡			1.03 (0.65, 1.64)	0.892		
Wild type	59	46				
Mutation	46	33				
NRAS‡			0.75 (0.18, 3.11)	0.690		
Wild type	103	77				
Mutation	2	2				
BRAF‡			2.53 (1.07, 6.00)	0.034*	2.49 (1.04, 5.96)	0.041*
Wild type	97	73				
Mutation	8	6				
MMR status‡			4.06 (1.44, 11.5)	0.008*	3.83 (1.24, 11.8)	0.019*
MSS	101	75				
MSI-high	4	4				
TMB‡			1.13 (0.67, 1.92)	0.648		
Low	83	60				
High	22	19				
HER2			0.73 (0.33, 1.61)	0.433	0.82 (0.35, 1.94)	0.652
Negative	96	72				
Positive	9	7				

†, tumors located at the descending colon, sigmoid colon, and rectum were defined as left-sided colorectal cancer. ‡, KRAS, NRAS, and BRAF mutation, MMR status, and TMB were tested using next-generation sequencing. The cut-off value for TMB-high was 10 mutations/Megabase. *, P value <0.05. HR, hazard ratio; BRAF, B-Raf Proto-Oncogene; ECOG, European Cooperative Oncology Group score; HER2, human epidermal growth factor receptor-2; KRAS, Kirsten ras oncogene homolog; MMR, mismatch repair; MSI, microsatellite instability; MSS, microsatellite stable; NRAS, neuroblastoma RAS viral oncogene homolog; TMB, tumor mutational burden.

Table 5 Univariate cox regression analyses of clinicopathological factors for the overall survival

Variables	No. of patients (n=105)	No. of events (n=40)	Univariate		Multivariate	
			HR (95% CI)	P	HR (95% CI)	P
Age			1.00 (0.98, 1.03)	0.758	1.00 (0.97, 1.02)	0.799
Sex			1.18 (0.61, 2.29)	0.620	0.95 (0.46, 1.97)	0.895
Male	65	26				
Female	40	14				
ECOG			4.27 (1.74, 10.5)	0.002*	6.05 (1.98, 18.5)	0.002*
0–1	96	34				
≥2	9	6				

Table 5 (*continued*)

Table 5 (*continued*)

Variables	No. of patients (n=105)	No. of events (n=40)	Univariate		Multivariate	
			HR (95% CI)	P	HR (95% CI)	P
Location			0.66 (0.33, 1.32)	0.238	0.55 (0.24, 1.25)	0.152
Colon	71	29				
Rectum	34	11				
Sidedness			0.78 (0.39, 1.56)	0.474	1.06 (0.46, 2.45)	0.884
Right	23	11				
Left	82	29				
Differentiation	(n=83)	(n=35)				
Well	8	2	Reference			
Moderate	66	26	1.41 (0.33, 5.97)	0.640		
Poor	9	7	2.52 (0.50, 12.6)	0.260		
KRAS‡			1.09 (0.58, 2.07)	0.787		
Wild type	59	23				
Mutation	46	17				
NRAS‡			1.62 (0.22, 11.9)	0.634		
Wild type	103	39				
Mutation	2	1				
BRAF‡			2.70 (0.93, 7.80)	0.067	3.06 (1.03, 9.06)	0.043*
Wild type	97	36				
Mutation	8	4				
MMR status‡			1.68 (0.51, 5.55)	0.394	2.51 (0.59, 10.7)	0.212
MSS	101	37				
MSI-high	4	3				
TMB‡			1.02 (0.50, 2.09)	0.962		
Low	83	30				
High	22	10				
HER2			1.50 (0.57, 3.90)	0.411	1.56 (0.56, 4.34)	0.394
Negative	96	35				
Positive	9	5				

†, tumors located at the descending colon, sigmoid colon, and rectum were defined as left-sided colorectal cancer. ‡, KRAS, NRAS, and BRAF mutation, MMR status, and TMB were tested using next-generation sequencing. The cut-off value for TMB-high was 10 mutations/Megabase. *, P value <0.05. HR, Hazard ratio; BRAF, B-Raf Proto-Oncogene; ECOG, European Cooperative Oncology Group score; HER2, human epidermal growth factor receptor-2; KRAS, Kirsten ras oncogene homolog; MMR, mismatch repair; MSI, Microsatellite instability; MSS, microsatellite stable; NRAS, neuroblastoma RAS viral oncogene homolog; TMB, tumor mutational burden.

standardized, partly because the results appear to differ depending on the detection method, which may include IHC and FISH or silver in situ hybridization (SISH). In CRC tissues, HER2 overexpression occurs through mechanisms distinct from those inducing *HER2* gene amplification, and HER2 overexpression is detected via IHC more frequently than *HER2* gene amplification (22,26,27). In CRC, false positives due to the low prevalence of HER2 overexpression or amplification could be one of the reasons for the differences in reported results.

Comparison with similar research

Notably, there is no consensus on the prognostic value of HER2 overexpression yet. Feng *et al.* reported that HER2 overexpression was associated with TP53 mutation and that adjuvant 5-fluorouracil prolonged OS in patients with HER2-positive Stage II CRC (32). In the PETACC-8 trial, ERBB2 alterations, including mutation and overexpression/amplification, were associated with a poor prognosis in the adjuvant setting, with shorter times to recurrence and shorter OS (33). However, HER2 overexpression/amplification in early-stage CRC has also been reported not to impact OS (34,35). In patients with mCRC in a palliative care setting, HER2 overexpression/amplification was associated with resistance to chemotherapy, and HER2 has therefore been considered a negative prognostic factor (23,36-39). However, when analyzing the data of 3,256 patients from the QUASAR, FOCUS, and PICCOLO trials, Richman *et al.* found no difference in OS and PFS among patients with and without HER2 overexpression/amplification (19). These findings are consistent with those of the present study. In the study, the status of HER2 expression was not an independent prognostic factor to PFS to first-line chemotherapy and OS in the univariate and multivariate analyses.

Explanations of findings

HER2 is downstream of the EGFR pathway and has been reported to activate the PI3K/AKT and RAS/RAF/MEK/ERK axis independently of EGFR, resulting in tumor progression (36,40-44). Persistent activation of HER2 and downstream pathways by HER-2 overexpression/amplification is considered one of the resistance mechanisms to anti-EGFR treatment (i.e., cetuximab or panitumumab) (23,25,36-39,45,46). In our analysis, most patients were treated with bevacizumab-containing chemotherapy as the first-line (90/105, 85.7%) and second-line (47/64, 73.4%) treatment regimens. Although both EGFR and HER2 are expressed in cancer cells, VEGF is involved in vascular proliferation in the tumor environment (47) but was not assessed in this study. VEGF expression could be why there was no difference between the HER2-positive and -negative groups in the survival analyses. Thus, while HER2 overexpression or amplification may be a predictive factor for anti-EGFR treatment, it does not appear to be a prognostic factor for mCRC.

In addition to testing for EGFR or RAS mutation, assessment of HER2 overexpression/amplification is needed to identify patients who may be less responsive to anti-EGFR antibody treatment and may benefit from treatment with other drugs (i.e., anti-VEGF antibody). However, in this study, only one of the patients with HER2-positive tumors was administered cetuximab. All the others were administered bevacizumab as a first-line treatment, and comparisons of the efficacy of cetuximab and bevacizumab were not conducted.

Limitations

This study had several limitations. First, this study had a small sample size and was retrospective in nature; our results should therefore be confirmed in a prospective study. Second, only Asian patients with mCRC were enrolled in the study, limiting the generalizability because of differences in the molecular profiles and clinical features between Western and Eastern patients with mCRC. Third, the analyses did not include patients who received anti-HER2-directed therapy.

Conclusions

There were no statistically significant differences in tumor response to first- and second-line chemotherapy, PFS, or OS in patients with mCRC with HER2-negative or -positive tumors. These findings suggest that HER2 overexpression need not be considered when choosing regimens as the current first- and second-line treatments.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-375/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-375/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Institutional Review Board of the Samsung Medical Center in Seoul (No. 2022-12-067), and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). As this study was performed retrospectively based on existing medical records, the requirement for written consent from the patients was waived by the IRB.

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