HER2 status is positively associated with vessel invasion of colorectal cancer: a retrospective large cohort study.

Mingdian Wang

Sun Yat-Sen University Cancer Center

Xiang Wang

Hefei Second People's Hospital

Yiwei Li

Fudan University Shanghai Cancer Center

Qingguo Li

Fudan University Shanghai Cancer Center

Sanjun Cai

Fudan University Shanghai Cancer Center

Xinxiang Li

Fudan University Shanghai Cancer Center

Maoguang Ma (✉ mamaoguang@shca.org.cn)

Fudan University

Research Article

Keywords: Colorectal cancer, HER2, immunohistochemistry, vessel invasion

Posted Date: March 7th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1415627/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Purpose HER2 positive colorectal cancer was drew increasing attention in recent years, accumulated evidence showed HER2 positive metastatic colorectal cancer could benefit from HER2 targeted therapy. While HER2 expression and the relationship between HER2 status and clinicopathological characteristics of overall colorectal cancer remains largely unknown. The aim of this study was to evaluate the HER2 expression in colorectal cancer and compare the clinicopathological features between HER2 positive and HER2 negative colorectal cancer.

Methods We retrospectively analyzed 3910 primary colorectal cancer patients treated in our institution from January 2016 to December 2019. Pathology reports after surgery were collected to provide information about HER2 status and other clinicopathological characteristics.

Results We identified 3347 HER2 negative and 79 HER2 positive colorectal cancer patients in our cohort. Chi-square test showed that vessel invasion was significantly more common in HER2 positive colorectal cancer patients. Crude analysis showed HER2 positive was associated with vessel invasion in colorectal cancer [OR and 95% CI 0.534 (0.341, 0.835), $p=0.006$]. After adjusting for N stage, a significant association was still observed between HER2 status and vessel invasion in colorectal cancer [OR and 95% CI 0.550 (0.322, 0.941), $p=0.029$].

Conclusion Our findings indicate that the rate of HER2 positivity in colorectal cancer was relatively low and HER2 status was strongly associated with vessel invasion in colorectal cancer patients.

Introduction

Human epidermal growth factor receptor 2 (HER2) is one of the member of the EGFR family of receptor tyrosine kinases[1]. Former studies had proved that HER2 overexpression is closely related with tumorigenesis and progression[2–4]. In addition, HER2 overexpressed in about 30% of breast cancer and 20% of advanced gastric cancer[5–8]. Based on the evidence from previous clinical trials, HER2 had been well-established as a therapeutic target in breast cancer and gastric cancer[9–13].

In recent years, many studies revealed that HER2 is a promising target in HER2-amplified metastatic colorectal cancer (CRC) [14–16]. Moreover, HER2 could be a negative biomarker for EGFR-targeted treatments in CRC[17]. However, most of current researches were focused on HER2 positive metastatic CRC (mCRC), the clinical and pathological features of overall HER2 positive CRC remains largely unknown.

In this retrospective study, we aimed to compare the clinical and pathological features between HER2 negative and HER2 positive CRC and provide meaningful information about HER2 positive CRC.

Methods

Patients

Patients newly diagnosed with CRC between January 2016 and December 2019 were retrospectively analyzed in this study. The inclusion criteria were as follows: (1) primary CRC with radical resection. (2) primary CRC with complete records of clinical and pathological data, including sex, age, T stage, N stage, distant metastasis, vessel invasion, perineural invasion, tumor differentiation and HER2 status. (3) primary CRC without neoadjuvant treatment. (4) primary CRC without other severe disease, especially cancer.

HER2 testing

HER2 status was measured by immunohistochemistry which was evaluated according to the HERACLES criteria (IHC score 0: no staining or staining in $\leq 10\%$ of cells; IHC score 1+: faint staining or moderate staining $\leq 50\%$ of cells or intense staining $\leq 10\%$ cells; IHC score 2+: moderate staining in $\geq 50\%$ of cells; IHC score 3+: intense staining in $\geq 50\%$ of cells. In situ hybridization (ISH) was mandatory when IHC score 2+. HER2 positivity, defined as IHC score 3+ and ISH HER2: CEP17 ratio higher than two in more than 50% of cells).

Only IHC score 0-1+ was considered HER2 negative and IHC score 3+ was considered HER2 positive in this study due to ISH of CRC was not routinely performed in our institute.

Statistical analysis

SPSS version 23.0 was recruited to conduct all statistical analysis. Student's *t* test was used to compare differences of continuous variables between HER2 negative and HER2 positive groups. The chi-square test or Fisher's exact test was used to compare categorical variables between HER2 negative and HER2 positive groups. Univariate and multivariate logistic regression models were applied to assess the influence of HER2 status on clinical and pathological characteristics by calculating the odd ratios and their corresponding 95% confidence intervals (CIs). $P \leq 0.05$ was considered to be statistically significant.

Results

We collected 4493 CRC patients treated in our department from January 2016 to December 2019. Among them, 96 were recurrent CRC cases, 404 patients co-exist with other severe diseases or received neoadjuvant treatment (12 with lung cancer history, 25 with breast cancer history, 17 with renal cancer history, 350 received neoadjuvant chemotherapy or radiotherapy) and 85 cases without IHC results of HER2 for unknown reasons. 3910 primary CRC cases with complete clinical and pathological data were enrolled in this study at last (Fig. 1).

The results of HER2 status tested by IHC were shown in Table 1. 2425 cases were IHC score 0, 922 cases were IHC score 1+, 484 cases were IHC score 2+ and 79 cases were IHC score 3+. As ISH of HER2 was not routinely performed in our institute, we could not estimate accurate HER2 status of the 484 cases whose

IHC results were score 2+. Therefore, 3347 cases were regarded as HER2 negative CRC and 79 as HER2 positive CRC according to the HERACLES criteria.

Patient characteristics were shown in Table 2. The average age was 58.29 and 60.43 years old in HER2 positive and HER2 negative group respectively. In HER2 positive group, there were 43 men (54.4%) and 36 women (45.6%); in HER2 negative group, there were 2079 men (62.1%) and 1268 women (37.9%). As for T stage, there were 7 T1 (8.9%), 9 T2 (11.4%), 52 T3 (65.8%) and 11 T4 (13.9%) cases in HER2 positive group, 167 T1 (5%), 475 T2 (14.2%), 2197 T3 (65.6%) and 508 T4 (15.2%) cases in HER2 negative group. With regard to N stage, there were 36 N0 (45.6%), 37 N1 (34.2%) and 16 N2 (20.3%) cases in HER2 positive group, 1842 N0 (55%), 924 N1 (27.6%) and 581 N2 (17.4%) cases in HER2 negative group. 10 patients (12.7%) in HER2 positive group and 498 patients (14.9%) in HER2 negative group with distant metastasis. For TNM stage, there were 10 stage I (12.7%), 23 stage II (29.1%), 36 stage III (45.6%) and 10 stage IV (12.7%) cases in HER2 positive group, 487 stage I (14.6%), 1207 stage II (36%), 1158 stage III (34.6%) and 495 stage IV (14.8%) cases in HER2 negative group. 42 cases (53.2%) in HER2 positive group and 1263 cases (37.7%) in HER2 negative group with vessel invasion. 32 patients (40.5%) in HER2 positive group and 1116 patients (33.3%) in HER2 negative group with perineural invasion. 3 cases in HER2 positive group and 177 cases in HER2 negative group were high differentiation tumor. Chi-square analysis showed significant differences of vessel invasion between HER2 positive and HER2 negative group ($p = 0.005$).

Logistic regression univariate and multivariate analysis were used to analyze the associations between HER2 status and other clinical and pathological characteristics. On crude analysis, HER2 positive CRC patients were more likely to with vessel invasion, OR and 95% CI 0.534 (0.341, 0.835), $p = 0.006$. After adjusting for N stage, a similar association was seen, OR and 95% CI 0.550 (0.322, 0.941), $p = 0.029$. While sex, T stage, N stage, distant metastasis, TNM stage, perineural invasion and tumor differentiation were not showed significant association with HER2 status (Table 3).

Discussion

The diagnostic criterion for HER2 positivity in CRC have not reached an agreement in worldwide. The rate of HER2 positivity in CRC varied widely from different researches due to inconsistent diagnostic criteria[18].

In this study, we adopted the HERACLES criteria which was proposed by Valtorta and his colleagues.[19] They established an archival test cohort which was conducted on formalin-fixed paraffin-embedded archival samples by three pathologists and concluded an agreement by collegial review and discussion, thus formulated a diagnostic algorithm for HER2 positivity in CRC, referred to as HERACLES Diagnostic Criteria. Then, the clinical validation cohort was established on KRAS 12/13 wild-type mCRC patients to validate the accuracy of this criteria.

HER2 expression in CRC can also be detected by molecular techniques except for IHC and ISH. Shimada Y et al proved that Comprehensive genomic sequencing (CGS) has the same utility as IHC and ISH for

detecting HER2-positive CRC patients[20]. Nakamura Y et al demonstrated that circulating tumor DNA (ctDNA) as an efficient marker for predicting *HER2*-amplified mCRC in clinical practice[21].

Some clinical trials had acquired promising results regarding HER2 targeted therapy in mCRC. The most well-known studies were HERACLES and MyPathway[22, 23]. HERACLES study preliminary proved that trastuzumab combined with lapatinib was effective in treating *KRAS* exon 2 wild type, HER2 positive mCRC (response rate was 30%, 4% for complete response and 26% for partial response). MyPathway study showed that pertuzumab plus trastuzumab was well tolerated and effective in treatment-refractory HER2-amplified mCRC (response rate was 32%, 2% for complete response and 30% for partial response). Grelly et al summarized 9 completed or ongoing clinical trials concerning HER2-targeted therapy in mCRC[24]. Though HER2 targeted therapy showed promising results in mCRC patients, the prognostic role of HER2 in CRC remains unclear, further large cohort studies with stratified and long-term follow up date were required to elucidate this point.

Several previous studies also analyzed the association between HER2 status and pathological characteristics in CRC patients. Zhang et al reported that HER2 status significantly associated with T stage and TNM stage in CRC, but not associated with lymphovascular invasion[25]. Seo et al reported that HER2 amplification was not associated with any pathological variables except tumor location in the rectum[26].

In conclusion, our study demonstrated that the rate of HER2 positive in CRC was relatively low and HER2 status was strongly associated with vessel invasion in CRC patients.

Declarations

Funding

None

Conflicts of Interests

The authors declare no potential conflicts of interest.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Mingdian Wang, Xiang Wang and Yiwei Li. The first draft of the manuscript was written by Maoguang Ma and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of FUSCC (Shanghai, China).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

References

1. Cho, H. S., Mason, K., Ramyar, K. X., Stanley, A. M., Gabelli, S. B., Denney, D. W., Jr. & Leahy, D. J. (2003) Structure of the extracellular region of HER2 alone and in complex with the Herceptin Fab, *Nature*. **421**, 756–60.
2. Moasser, M. M. (2007) The oncogene HER2: its signaling and transforming functions and its role in human cancer pathogenesis, *Oncogene*. **26**, 6469–87.
3. Vranić, S., Bešlija, S. & Gatalica, Z. (2021) Targeting HER2 expression in cancer: New drugs and new indications, *Bosnian journal of basic medical sciences*. **21**, 1–4.
4. Neve, R. M., Lane, H. A. & Hynes, N. E. (2001) The role of overexpressed HER2 in transformation, *Annals of oncology: official journal of the European Society for Medical Oncology*. **12 Suppl 1**, S9-13.
5. Harbeck, N. & Gnant, M. (2017) Breast cancer, *Lancet (London, England)*. **389**, 1134–1150.
6. Incorvati, J. A., Shah, S., Mu, Y. & Lu, J. (2013) Targeted therapy for HER2 positive breast cancer, *Journal of hematology & oncology*. **6**, 38.
7. Boku, N. (2014) HER2-positive gastric cancer, *Gastric cancer: official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association*. **17**, 1–12.
8. Gravalos, C. & Jimeno, A. (2008) HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target, *Annals of oncology: official journal of the European Society for Medical Oncology*. **19**, 1523–9.
9. Meric-Bernstam, F., Johnson, A. M., Dumbrava, E. E. I., Raghav, K., Balaji, K., Bhatt, M., Murthy, R. K., Rodon, J. & Piha-Paul, S. A. (2019) Advances in HER2-Targeted Therapy: Novel Agents and Opportunities Beyond Breast and Gastric Cancer, *Clinical cancer research: an official journal of the American Association for Cancer Research*. **25**, 2033–2041.
10. Kunte, S., Abraham, J. & Montero, A. J. (2020) Novel HER2-targeted therapies for HER2-positive metastatic breast cancer, *Cancer*. **126**, 4278–4288.
11. Shitara, K., Iwata, H., Takahashi, S., Tamura, K., Park, H., Modi, S., Tsurutani, J., Kadowaki, S., Yamaguchi, K., Iwasa, S., Saito, K., Fujisaki, Y., Sugihara, M., Shahidi, J. & Doi, T. (2019) Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive gastric cancer: a dose-expansion, phase 1 study, *The Lancet Oncology*. **20**, 827–836.

12. Tabernero, J., Hoff, P. M., Shen, L., Ohtsu, A., Shah, M. A., Cheng, K., Song, C., Wu, H., Eng-Wong, J., Kim, K. & Kang, Y. K. (2018) Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study, *The Lancet Oncology*. **19**, 1372–1384.
13. Doi, T., Shitara, K., Naito, Y., Shimomura, A., Fujiwara, Y., Yonemori, K., Shimizu, C., Shimoj, T., Kuboki, Y., Matsubara, N., Kitano, A., Jikoh, T., Lee, C., Fujisaki, Y., Ogitani, Y., Yver, A. & Tamura, K. (2017) Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: a phase 1 dose-escalation study, *The Lancet Oncology*. **18**, 1512–1522.
14. Ross, J. S., Fakih, M., Ali, S. M., Elvin, J. A., Schrock, A. B., Suh, J., Vergilio, J. A., Ramkissoon, S., Severson, E., Daniel, S., Fabrizio, D., Frampton, G., Sun, J., Miller, V. A., Stephens, P. J. & Gay, L. M. (2018) Targeting HER2 in colorectal cancer: The landscape of amplification and short variant mutations in ERBB2 and ERBB3, *Cancer*. **124**, 1358–1373.
15. Siena, S., Sartore-Bianchi, A., Marsoni, S., Hurwitz, H. I., McCall, S. J., Penault-Llorca, F., Srock, S., Bardelli, A. & Trusolino, L. (2018) Targeting the human epidermal growth factor receptor 2 (HER2) oncogene in colorectal cancer, *Annals of oncology: official journal of the European Society for Medical Oncology*. **29**, 1108–1119.
16. Sartore-Bianchi, A., Lonardi, S., Martino, C., Fenocchio, E., Tosi, F., Ghezzi, S., Leone, F., Bergamo, F., Zagonel, V., Ciardiello, F., Ardizzoni, A., Amatu, A., Bencardino, K., Valtorta, E., Grassi, E., Torri, V., Bonoldi, E., Sapino, A., Vanzulli, A., Regge, D., Cappello, G., Bardelli, A., Trusolino, L., Marsoni, S. & Siena, S. (2020) Pertuzumab and trastuzumab emtansine in patients with HER2-amplified metastatic colorectal cancer: the phase II HERACLES-B trial, *ESMO open*. **5**, e000911.
17. Sawada, K., Nakamura, Y., Yamanaka, T., Kuboki, Y., Yamaguchi, D., Yuki, S., Yoshino, T., Komatsu, Y., Sakamoto, N., Okamoto, W. & Fujii, S. (2018) Prognostic and Predictive Value of HER2 Amplification in Patients With Metastatic Colorectal Cancer, *Clinical colorectal cancer*. **17**, 198–205.
18. De Cuyper, A., Van Den Eynde, M. & Machiels, J. P. (2020) HER2 as a Predictive Biomarker and Treatment Target in Colorectal Cancer, *Clinical colorectal cancer*. **19**, 65–72.
19. Valtorta, E., Martino, C., Sartore-Bianchi, A., Penault-Llorca, F., Viale, G., Risio, M., Rugge, M., Grigioni, W., Bencardino, K., Lonardi, S., Zagonel, V., Leone, F., Noe, J., Ciardiello, F., Pinto, C., Labianca, R., Mosconi, S., Graiff, C., Aprile, G., Frau, B., Garufi, C., Loupakis, F., Racca, P., Tonini, G., Lauricella, C., Veronese, S., Truini, M., Siena, S., Marsoni, S. & Gambacorta, M. (2015) Assessment of a HER2 scoring system for colorectal cancer: results from a validation study, *Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc*. **28**, 1481-91.
20. Shimada, Y., Yagi, R., Kameyama, H., Nagahashi, M., Ichikawa, H., Tajima, Y., Okamura, T., Nakano, M., Nakano, M., Sato, Y., Matsuzawa, T., Sakata, J., Kobayashi, T., Nogami, H., Maruyama, S., Takii, Y., Kawasaki, T., Homma, K. I., Izutsu, H., Kodama, K., Ring, J. E., Protopopov, A., Lyle, S., Okuda, S., Akazawa, K. & Wakai, T. (2017) Utility of comprehensive genomic sequencing for detecting HER2-positive colorectal cancer, *Human pathology*. **66**, 1–9.

21. Nakamura, Y., Okamoto, W., Kato, T., Esaki, T., Kato, K., Komatsu, Y., Yuki, S., Masuishi, T., Nishina, T., Ebi, H., Sawada, K., Taniguchi, H., Fuse, N., Nomura, S., Fukui, M., Matsuda, S., Sakamoto, Y., Uchigata, H., Kitajima, K., Kuramoto, N., Asakawa, T., Olsen, S., Odegaard, J. I., Sato, A., Fujii, S., Ohtsu, A. & Yoshino, T. (2021) Circulating tumor DNA-guided treatment with pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer: a phase 2 trial, *Nature medicine*. **27**, 1899–1903.
22. Sartore-Bianchi, A., Trusolino, L., Martino, C., Bencardino, K., Lonardi, S., Bergamo, F., Zagonel, V., Leone, F., Depetris, I., Martinelli, E., Troiani, T., Ciardiello, F., Racca, P., Bertotti, A., Siravegna, G., Torri, V., Amatu, A., Ghezzi, S., Marrapese, G., Palmeri, L., Valtorta, E., Cassingena, A., Lauricella, C., Vanzulli, A., Regge, D., Veronese, S., Comoglio, P. M., Bardelli, A., Marsoni, S. & Siena, S. (2016) Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial, *The Lancet Oncology*. **17**, 738–746.
23. Meric-Bernstam, F., Hurwitz, H., Raghav, K. P. S., McWilliams, R. R., Fakih, M., VanderWalde, A., Swanton, C., Kurzrock, R., Burris, H., Sweeney, C., Bose, R., Spigel, D. R., Beattie, M. S., Blotner, S., Stone, A., Schulze, K., Cuchelkar, V. & Hainsworth, J. (2019) Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study, *The Lancet Oncology*. **20**, 518–530.
24. Greally, M., Kelly, C. M. & Cercek, A. (2018) HER2: An emerging target in colorectal cancer, *Current problems in cancer*. **42**, 560–571.
25. Zhang, X., Wu, J., Wang, L., Zhao, H., Li, H., Duan, Y., Li, Y., Xu, P., Ran, W. & Xing, X. (2020) HER2 and BRAF mutation in colorectal cancer patients: a retrospective study in Eastern China, *PeerJ*. **8**, e8602.
26. Seo, A. N., Kwak, Y., Kim, D. W., Kang, S. B., Choe, G., Kim, W. H. & Lee, H. S. (2014) HER2 status in colorectal cancer: its clinical significance and the relationship between HER2 gene amplification and expression, *PloS one*. **9**, e98528.

Tables

Table 1. Demographics and clinical characteristics of patients in this study.

Characteristics	IHC(-) n(%) / mean±sd	IHC(1+) n(%) / mean±sd	IHC(2+) n(%) / mean±sd	IHC(3+) n(%) / mean±sd
Age(yaer)	60.35±11.89	60.51±11.61	60.24±11.72	58.29±10.39
Sex				
Male	1480(60)	599(65)	318(65.7)	43(54.4)
Female	945(40)	323(35)	166(34.3)	36(45.6)
T stage				
T1	133(5.5)	34(3.7)	22(4.5)	7(8.9)
T2	347(14.3)	128(13.9)	67(13.8)	9(11.4)
T3	1566(64.6)	631(68.4)	335(69.2)	52(65.8)
T4	379(15.6)	129(14)	60(12.4)	11(13.9)
N stage				
N0	1318(54.4)	524(56.8)	267(55.2)	36(45.6)
N1	670(27.6)	254(27.6)	139(28.7)	27(34.2)
N2	437(18)	144(15.6)	78(16.1)	16(20.3)
Distant metastasis				
Yes	2084(85.9)	765(83)	390(80.6)	69(87.3)
No	341(14.1)	157(17)	94(19.4)	10(12.7)
TNM stage				
I	360(14.9)	127(13.8)	61(12.6)	10(12.7)
II	856(35.3)	351(38.1)	181(37.4)	23(29.1)
III	869(35.8)	289(31.3)	148(30.6)	36(45.6)
IV	340(14)	155(16.8)	94(19.4)	10(12.7)
Vessel invasion				
Yes	1489(61.4)	595(64.5)	310(64)	37(46.8)
No	936(38.6)	327(35.5)	174(36)	42(53.2)
Perineural invasion				
Yes	1616(66.6)	615(66.7)	305(63)	47(59.5)
No	809(33.4)	307(33.3)	179(37)	32(40.5)
Tumor differentiation				

High	2293(94.6)	877(95.1)	455(94)	76(96.2)
Poor-moderate	132(5.4)	45(4.9)	29(6)	3(3.8)
Total	2425(62)	922(23.6)	484(12.4)	79(2)

Table 2. Number of patients in HER2 positive and HER2 negative groups respectively.

	HER2 positive n(%) / mean±sd	HER2 negative n(%) / mean±sd	Statistic	<i>P</i>
Age(year)	58.29±10.391	60.43±11.89	-1.587	0.113
Sex				
Male	43 (54.4)	2079 (62.1)	1.933	0.164
Female	36 (45.6)	1268 (37.9)		
T stage				
T1	7 (8.9)	167 (5)	2.717	0.43
T2	9 (11.4)	475 (14.2)		
T3	52 (65.8)	2197 (65.6)		
T4	11 (13.9)	508 (15.2)		
N stage				
N0	36 (45.6)	1842 (55)	2.833	0.243
N1	27 (34.2)	924 (27.6)		
N2	16 (20.3)	581 (17.4)		
Distant metastasis				
Yes	10 (12.7)	498 (14.9)	0.301	0.583
No	69 (87.3)	2849 (85.1)		
TNM stage				
I	10 (12.7)	487 (14.6)	4.132	0.248
II	23 (29.1)	1207 (36)		
III	36 (45.6)	1158 (34.6)		
IV	10 (12.7)	495 (14.8)		
Vessel invasion				
Yes	42 (53.2)	1263 (37.7)	7.791	0.005
No	37 (46.8)	2084 (62.3)		
Perineural invasion				
Yes	32 (40.5)	1116 (33.3)	1.772	0.183
No	47 (59.5)	2230 (66.7)		
Tumor differentiation				

High	3 (3.8)	177 (5.3)	0.798	0.396
Poor-moderate	76 (96.2)	3170 (94.7)		

Table 3. Odds ratios (OR) (with 95% CI) of HER2 positive relative to HER2 negative by different characteristics of CRC patients.

		Crude		Adjusted	
		OR (95% CI)	P	OR (95% CI)	P
Sex	Male	Ref.			
	Female	0.729 (0.465, 1.141)	0.166	\	
T stage	T1-T2	Ref.			
	T3-T4	1.072 (0.615, 1.868)	0.806	\	
N stage	N0	Ref.		Ref.	
	N1-N2	0.684 (0.437, 1.071)	0.097	0.946 (0.553, 1.619)	0.839
Distant metastasis	Yes	Ref.			
	No	1.206 (0.617, 2.357)	0.584	\	
TNM stage	I -II	Ref.			
	III-IV	0.700 (0.445, 1.100)	0.122	\	
Vessel invasion	Yes	Ref.		Ref.	
	No	0.534 (0.341, 0.835)	0.006	0.550 (0.322, 0.941)	0.029
Perineural invasion	Yes	Ref.			
	No	0.735 (0.466, 1.158)	0.184	\	
Tumor differentiation	High	Ref.			
	Poor-moderate	1.415 (0.442, 4.528)	0.559	\	

Figures

Figure 1

Flow diagram of the patient selection process.