Utilization of genetic biomarkers testing and its associated factors in advanced colorectal cancer patients in China: a nationwide multicenter clinical epidemiological study

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Background: Biomarkers are a key tool in early detection, prognostication, survival, and predicting treatment response of colorectal cancer (CRC). However, little is known about biomarker testing for CRC patients in real-life clinical practice in China. This study aimed to address the usage of biomarker testing and analyze factors related to its acceptance among Chinese patients with advanced CRC.

Methods: A multicenter, cross-sectional, hospital-based clinical epidemiology study was conducted from

March 2020 to March 2021. Nineteen hospitals were selected in seven geographical regions of China using stratified, multistage, nonrandomized cluster sampling. Data on demographics and clinical characteristics of each eligible CRC patient in stage III or IV diseases were recorded based on the patients' self-reporting and/or medical records. In addition, information on whether biomarker testing [*RAS*, *BRAF*, and microsatellite instability (MSI)] was performed, the results and timing for performing biomarker testing, and the reasons for refusing biomarker testing were also recorded. Univariate and multivariate logistic regression were conducted to explore the potential factors of biomarker testing.

Results: A total of 4,526 patients were enrolled in the study, of whom 41.4%, 36.1%, and 28.2% underwent *RAS*, *BRAF*, and MSI testing, respectively. *RAS*, *BRAF*, and high-level MSI (MSI-high) mutation rates in Chinese patients with advanced CRC were 37.0%, 9.9%, and 8.1%, respectively. The logistic regression analysis revealed that the treating hospital, age at diagnosis, education, family income, tumor site, history of chemotherapy and radiotherapy, and metastases were dependent factors affecting the utilization of biomarker testing in advanced CRC in China (P<0.005).

Conclusions: The biomarker testing rate, especially MSI testing, is less prevalent in clinical practice for patients with advanced CRC in China. Our findings may guide the formulation of biomarker testing of CRC strategies in China and other low-income countries.

Keywords: Colorectal cancer (CRC); biomarker; *RAS*; *BRAF*; microsatellite instability (MSI)

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Introduction

Colorectal cancer (CRC) is the third most prevalent malignancy worldwide, with an estimated 1.9 million new cases and 935,173 deaths occurring in 2020 (1). Although CRC incidence and mortality rates have been steady or declining in Western countries for the past two to three decades, both rates have been significantly growing in many developing countries, such as China and Brazil, due to westernization (2). According to China's most recent national cancer registry, approximately 408,000 new cases of CRC and 195,600 CRC-related deaths occurred in 2016 (3). Even though the age-standardized 5-year survival rate has increased from 47.2% in 2003–2005 to 56.9% in 2012–2015 (4), it is still approximately 10% lower than that in the United States (5). Of more concern, by the time of initial diagnosis, more than half (51.4%) of Chinese CRC patients had progressed to an advanced stage, which dramatically reduced their survival (6).

In China, the current therapeutic options for CRC vary, with therapy allocation largely dependent on available resources, the patient's financial situation, and the tumor burden (7). With the development of next-generation sequencing (NGS) and medicine design techniques in recent decades, several of the following gene-based biomarkers have helped clinicians make optimal treatment decisions: *NRAS*, *KRAS*, and *BRAF* mutations, and microsatellite instability (MSI) or mismatch repair (MMR). They all play an increasingly critical role in the early diagnosis, targeted drug identification, and drug reactions of patients with CRC.

Monoclonal antibodies against epidermal growth factor receptors (EGFRs), such as cetuximab and panitumumab, have been proven to significantly improve overall survival (OS) in patients with advanced CRC (8,9). *RAS* mutations have been recognized as a predictor of EGFR-targeted therapy resistance, as confirmed by the OPUS and CCRYSTAL trials (10,11). In addition, *BRAF* mutations are well-recognized poor prognostic factors for CRC (12,13). Furthermore, recent research has found that CRC patients with varying MSI levels have diverse drug reactivity and sensitivity, hinting that MSI status could be a predictive marker for clinical therapy (14,15).

Although previous studies have been conducted to estimate biomarker prevalence in China, most of them have only focused on a single hospital with a relatively small sample size (16,17). Here, for the first time, our study aims to estimate the percentage of advanced CRC patients in China who have undergone biomarker testing, the mutation prevalence of different molecular subtypes,

and identify the barriers limiting testing. We hypothesized that these investigations might yield recommendations to update treatment guidelines and develop tailored treatment strategies for patients with advanced CRC in China and other low- and middle-income countries. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-988/rc).

Methods

This study was approved by the independent review board of Henan Cancer Hospital (No. 2019273), and all patients provided signed informed consent form. The study was conducted in accordance with the Declaration of Helsinki Declaration (as revised in 2013).

Study design

We conducted a multicenter, cross-sectional, hospital-based clinical epidemiology study of advanced CRC in mainland China using stratified, multistage, nonrandomized cluster sampling.

Selection of hospitals

In brief, China was stratified into seven geographic regions according to the traditional administrative district definition: North, Northeast, Northwest, Central, Eastern, Southern, and Southwest. These regions encompass most of the geographic area of China's mainland and represent different levels of CRC burden (18). Two cities in each geographic region were selected through convenience sampling to ensure the national survey was representative. In each city, one or two leading tertiary cancer hospitals and one or two tertiary general hospitals that were considered representative of the regional resources available to patients were chosen based on their ability to provide comprehensive CRC therapy. Ultimately, nineteen tertiary hospitals (10 cancer hospitals and 9 general hospitals) were involved in the study.

Patient selection and pathologic diagnostic criteria

All eligible CRC patients in the selected hospitals were invited by the interviewer to participate current study. The inclusion criteria of the study were as follows: (I) patients were aged ≥18 years; (II) patients were able to consent to participate in the study; (III) patients had a pathologically confirmed diagnosis of stage III or IV CRC. Patients were excluded if they had severe physical, cognitive, and/or verbal impairments that interfered with the completion of the questionnaire. CRC staging was performed according to the 8th edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system (19).

Data collection and quality control

A designed case report form (CRF) was used to collect information on the enrolled patients, including demographic and medical history, medical experience with CRC diagnosis and treatment, and clinicopathological features (including pathological reports and biomarker status). The detailed information included: (I) basic demographic, such as age, gender, occupational situation, marital status, education, and annual household income of patients; (II) clinical information, such as cancer types (colon cancer, rectal cancer, and both), stage, and metastasis status at diagnosis; and (III) biomarker testing status, such as whether biomarker testing (*RAS*, *BRAF*, and MSI) was performed, the results and timing for performing biomarker testing, and the reasons for refusing biomarker testing. All completed questionnaires were checked immediately by the clerks to avoid any missing or invalid data.

Trained interviewers extracted the above information from the patients' self-report and/or medical records. Then, two data input clerks were recruited in each hospital to independently double-enter the data from the paper questionnaire into an electronic database. The completed databases were sent for validation by running EpiData, version 3.1 (EpiData Association, Odense, Denmark) software. Inconsistencies between the two databases were reported to the local interviewers for adjudication until the databases agreed.

Statistical analysis

All statistical analyses were performed utilizing SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA). The demographic and clinical characteristics of the patients were described by the mean and standard deviation (SD) of continuous variables or the percentage and proportion of categorical variables. The chi-square test was employed when comparing differences in the use of biomarker testing and mutation status between colon and rectal cancer.

Univariate and multivariate logistic regressions were conducted on the data of patients with complete information to explore predictor variables associated with biomarker testing acceptability. Variables with a P value <0.10 in the univariate model were entered into the multivariate model, and only those variables with a P value <0.05 were retained in the final multivariate model. Odds ratios (ORs) and adjusted ORs (AORs) with 95% confidence intervals (CIs) were calculated using Wald chi-square statistics. All tests were two-tailed tests with a significance level of 0.05, and all the missing data were excluded.

Results

A total of 4,589 advanced CRC patients across seven geographic regions of China's mainland were included in the study from March 2020 to March 2021. Sixty-three cases were excluded due to a lack of biomarker testing information. Ultimately, 4,526 cases (60.1±11.6 years) with complete information were included in the analysis. Of all cases, 2,059 (45.5%) were colon cancer, and 2,080 (46.0%) were recruited from cancer hospitals (*Table 1*).

Patient characteristics

Overall, the majority of patients were male (59.5%), received 7–12 years of schooling (55.1%), and had a lower family income [<50,000 Chinese yuan (CNY) per year] (57.5%). The mean age at first diagnosis was 58.7±11.8 years, 76.9% were diagnosed with late-stage (stage III or IV) cancer, and 62.2% had no metastases at the time of diagnosis (*Table 1*).

Biomarker testing in patients with advanced CRC

Clinicians recommended biomarker testing to 67.7% of all advanced CRC patients. However, less than half (46.2%) underwent at least one molecular test (*RAS*, *BRAF*, or MSI). Regarding tumor sites, we found that doctors advised biomarker testing to more colon cancer patients, and more colon cancer patients completed the test (P<0.001). Overall, *RAS* and *BRAF* testing was performed in approximately 41.4% and 36.1% of advanced CRC patients in China, respectively. The rate of MSI testing was only 28.2% in patients with advanced CRC, with a statistically significant difference between colon (30.4%) and rectal cancer patients (25.3%) (P=0.037) (*Table 2*).

Mutation of RAS, BRAF, and MSI in patients with advanced CRC

Of the 1,873 patients who underwent *RAS* testing, 607 (37.0%) had a positive *RAS* mutation status. A positive *BRAF* mutation status was found in 140 (9.9%) of the 1,632 patients who received *BRAF* testing. High-level MSI (MSI-H) and low-level MSI (MSI-L) tumors were found in 8.1% and 4.0% of advanced CRC patients, respectively (*Table 2*).

Factors affecting decision-making regarding the use of biomarker testing

We performed a logistic regression analysis of factors that might affect decision-making regarding the use of biomarker testing for advanced CRC patients. The findings revealed that biomarker testing was more common in patients who were treated at cancer hospitals (P<0.001), diagnosed at a younger age (<50 years old) (P=0.026), received higher education (more than 6 years) (P=0.005 and P<0.001), had a higher family income (≥100,000 CNY per year) (P=0.001), had a diagnosis of colon cancer (P=0.003), had a history of chemotherapy (P=0.001), had no history of radiotherapy (P=0.009), and had metastases (P<0.001). Sex, locality, and age at the time of the survey, TNM stage, and surgical history had no significant effect on decision-making regarding the use of biomarkers (P>0.05) (*Table 3*).

The time frame for biomarker testing

The time frame for biomarker detection varied considerably among Chinese patients with advanced CRC. Of the 2,092 patients who underwent biomarker testing, nearly one-third (32.6%) received testing after surgery, 24.5% after diagnosis, 19.2% before initial treatment, 18.3% after recurrence, and 5.4% before changing treatment regimens (*Figure 1*).

Reasons for refusing biomarker testing

Barriers to biomarker testing included the unaffordable price of the testing (23.7%), concerns about the effectiveness of targeted therapy (16.1%), and eagerness to start treatment (5.6%). Surprisingly, most patients (42.5%) did not participate in biomarker testing because they were not being informed of the availability of biomarker testing (*Figure 2*).

Table 1 Demographic and clinical characteristics of advanced CRC patients

Variables	All cases	Colon cancer	Rectal cancer	P value
All patients, n	4,526	2,059	2,467	
Type of treating hospital, n (%)				0.091
Cancer hospitals	2,080 (46.0)	918 (44.6)	1,162 (47.1)	
General hospitals	2,446 (54.0)	1,141 (55.4)	1,305 (52.9)	
Gender, n (%)				0.327
Males	2,693 (59.5)	1,209 (58.7)	1,484 (60.2)	
Females	1,833 (40.5)	850 (41.3)	983 (39.8)	
Age at current therapy				0.062
Mean ± SD, years	60.1±11.6	59.7±11.8	60.4±11.4	
<50 years, n (%)	749 (16.5)	364 (17.7)	385 (15.6)	
≥50 years, n (%)	3,777 (83.5)	1,695 (82.3)	2,082 (84.4)	
Age at initial diagnosis				0.075
Mean ± SD, years	58.7±11.8	58.3±12.0	59.0±11.6	
<50 years, n (%)	921 (20.3)	443 (21.5)	478 (19.4)	
≥50 years, n (%)	3,605 (79.7)	1,616 (78.5)	1,989 (80.6)	
Educational level, n (%)[†]				<0.001
≤6 years	1,312 (29.0)	538 (26.2)	774 (31.4)	
7–12 years	2,491 (55.1)	1,155 (56.2)	1,336 (54.2)	
>12 years	720 (15.9)	363 (17.7)	357 (14.5)	
Family income per year, n (%)				<0.001
<50,000 CNY	2,601 (57.5)	1,088 (52.8)	1,513 (61.3)	
50,000–99,999 CNY	1,278 (28.2)	654 (31.8)	624 (25.3)	
≥100,000 CNY	647 (14.3)	317 (15.4)	330 (13.4)	
Stage at diagnosis, n (%)				<0.001
Stage I	109 (2.4)	43 (2.1)	66 (2.7)	
Stage II	760 (16.8)	361 (17.5)	399 (16.2)	
Stage III	1,947 (43.0)	753 (36.6)	1,194 (48.4)	
Stage IV	1,534 (33.9)	833 (40.5)	701 (28.4)	
Unknown	176 (3.9)	69 (3.4)	107 (4.3)	
Metastases, n (%)				<0.001
Localized	2,813 (62.2)	1,147 (55.7)	1,666 (67.5)	
Liver only	635 (14.0)	362 (17.6)	273 (11.1)	
Lung only	178 (3.9)	70 (3.4)	108 (4.4)	
Liver and lung combination	191 (4.2)	98 (4.8)	93 (3.8)	
Others or unknown	709 (15.7)	382 (18.6)	327 (13.3)	

[†], the total number varies due to missing values. CRC, colorectal cancer; SD, standard deviation; CNY, Chinese yuan.

Table 2 Percentage of advanced CRC patients tested for *RAS*, *BRAF*, and MSI and mutant biomarker status

Variables	Total	Colon cancer	Rectal cancer	P value
Doctor recommend testing, n (%)[†]				<0.001
Yes	3,061 (67.7)	1,472 (71.6)	1,589 (64.5)	
No	1,460 (32.3)	585 (28.4)	875 (35.5)	
Complete any genetic testing, n (%)				<0.001
Yes	2,092 (46.2)	1,068 (51.9)	1,024 (41.5)	
No	2,434 (53.8)	991 (48.1)	1,443 (58.5)	
RAS tests, n/N (%)	1,873/4,526 (41.4)	953/2,059 (46.3)	920/2,467 (37.3)	0.167
RAS wild-type, n (%)	1,035 (63.0)	545 (64.7)	490 (61.3)	
RAS mutation, n (%)	607 (37.0)	298 (35.3)	309 (38.7)	
Unknown, n	231	110	121	
BRAF tests, n/N (%)	1,632/4,526 (36.1)	836/2,059 (40.6)	796/2,467 (32.3)	0.262
BRAF wild-type, n (%)	1,275 (90.1)	649 (88.9)	626 (91.4)	
BRAF mutation, n (%)	140 (9.9)	81 (11.1)	59 (8.6)	
Unknown, n	217	106	111	
MSI tests, n/N (%)	1,276/4,526 (28.2)	625/2,059 (30.4)	623/2,467 (25.3)	0.037
MSS, n (%)	910 (87.9)	436 (85.3)	448 (90.3)	
MSI-L, n (%)	41 (4.0)	21 (4.1)	20 (4.0)	
MSI-H, n (%)	84 (8.1)	54 (10.6)	28 (5.6)	
Unknown, n	241	114	127	

[†], the total number varies due to missing values. CRC, colorectal cancer; MSI, microsatellite instability; MSS, microsatellite stability; MSI-L, low-level MSI; MSI-H, high-level MSI.

Discussion

This study presents the results of 4,526 Chinese patients with advanced CRC. To the best of our knowledge, this is the first study at a national level in China to analyze biomarkers in patients with advanced CRC. We obtained information on critical markers in CRC patients and analyzed potential influencing factors. These real-world practice data will assist health providers in identifying personalized treatment plans for patients and ultimately reduce the disease burden of CRC.

Some leading guideline bodies, such as the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) (20-22), have recommended important markers for selecting personalized therapies for patients with CRC. In our analysis, less than half (41.4% for *RAS*, 36.1% for *BRAF*, and 28.2% for MSI) of patients with advanced CRC had biomarker testing, which was much lower than European rates (>90% for *RAS*, 66.9% for *BRAF*, and 41.4% for MSI) (23). There are two possible explanations for the low uptake of biomarker testing: one reason is that referring physicians disagree with the guideline recommendations and are unaware of the utility of biomarkers. Only 67.7% of physicians in this study recommended biomarker testing to patients. Of more concern, 18.3% of these patients only received biomarker evaluation after acquiring recurrent metastases, and 5.4% had biomarker testing on changing treatment regimens, contrary to existing clinical standards. Another reason for patients' hesitation in undergoing biomarker testing was related to financial concerns. Despite their physicians' advice, 23.7% of patients did not comply with treatment recommendations due to expense. Furthermore, this study revealed that patients in better financial situations received more biomarker testing than those in worse financial situations. These findings suggest

Table 3 Factors associated with the use of biomarker testing in advanced CRC patients in China

Variables	Had biomarker testing (n=2,092), n (%)	Univariate analysis		Multivariate analysis	
		OR (95% CI)	P value	AOR (95% CI)	P value
Treating hospital					
Cancer hospitals	1,190 (57.2)	Ref		Ref	
General hospitals	902 (36.9)	0.44 (0.38–0.49)	<0.001	0.39 (0.34–0.46)	<0.001
Age at survey day					
<50 years	426 (56.9)	Ref		–	
≥50 years	1,666 (44.1)	0.60 (0.51–0.70)	<0.001	–	–
Age at diagnosis					
<50 years	520 (56.5)	Ref		Ref	
≥50 years	1,572 (43.6)	0.60 (0.51–0.68)	<0.001	0.80 (0.66–0.97)	0.026
Geographic[†]					
Less developed areas	955 (47.4)	Ref		–	
Developed areas	1,137 (45.2)	0.92 (0.81–1.02)	0.141	–	–
Gender					
Males	1,253 (46.5)	Ref		–	
Females	839 (45.8)	0.97 (0.86–1.09)	0.617	–	–
Educational level					
≤6 years	471 (35.9)	Ref		Ref	
6–12 years	1,175 (47.2)	1.59 (1.38–1.82)	<0.001	1.30 (1.08–1.56)	0.005
>12 years	445 (61.8)	2.89 (2.39–3.48)	<0.001	2.12 (1.61–2.80)	<0.001
Family income per year					
<50,000 CNY	1,125 (43.3)	Ref		Ref	
50,000–99,999 CNY	583 (45.6)	1.10 (0.96–1.25)	0.163	0.99 (0.82–1.18)	0.872
≥100,000 CNY	384 (59.4)	1.92 (1.60–2.28)	<0.001	1.52 (1.19–1.94)	0.001
Doctor recommend					
No	107 (7.3)	Ref		Ref	
Yes	1,982 (64.8)	23.22 (18.80–28.60)	<0.001	23.61 (18.78–29.70)	<0.001
Tumor sites					
Colon	1,068 (51.9)	Ref		Ref	
Rectal	1,024 (41.5)	0.66 (0.58–0.74)	<0.001	0.79 (0.67–0.92)	0.003
Surgery					
No	399 (54.2)	Ref		–	
Yes	1,692 (44.7)	0.68 (0.58–0.80)	<0.001	–	–

Table 3 (*continued*)

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Variables	Had biomarker testing (n=2,092), n (%)	Univariate analysis		Multivariate analysis	
		OR (95% CI)	P value	AOR (95% CI)	P value
Adjuvant chemotherapy					
No	161 (26.5)	Ref		Ref	
Yes	1,930 (49.4)	2.71 (2.23–3.27)	<0.001	1.54 (1.21–1.96)	0.001
Adjuvant radiotherapy					
No	1,676 (47.7)	Ref		Ref	
Yes	415 (41.5)	0.78 (0.67–0.80)	<0.001	0.78 (0.64–0.94)	0.009
Stage at diagnosis					
I & II	291 (33.5)	Ref		–	
III & IV	1,737 (49.9)	1.98 (1.69–2.31)	<0.001	–	–
Metastases					
No	1,016 (36.1)	Ref		Ref	
Yes	1,066 (63.0)	3.01 (2.65–3.41)	<0.001	2.13 (1.82–2.49)	<0.001

†, less developed areas: Central, Northwest, Southwest, and Northeast; developed areas: East, South, Northern. CRC, colorectal cancer; OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval; CNY, Chinese yuan.

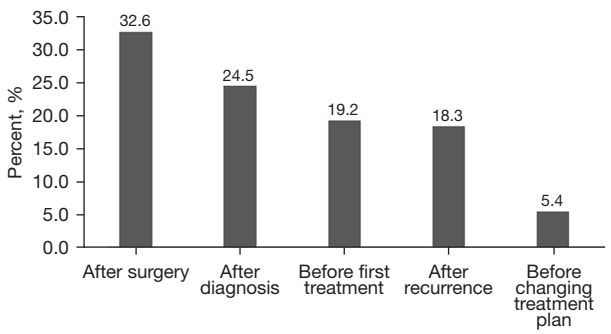

Figure 1 Time frame for performing biomarker testing in Chinese advanced colorectal cancer patients.

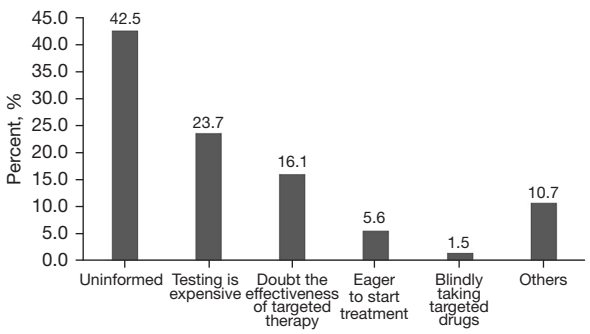

Figure 2 Reasons for refusing biomarker testing in Chinese advanced colorectal cancer patients.

that physicians at all levels need to be better educated on the most updated clinical guidelines. Moreover, policymakers should consider reducing the cost of key biomarker tests or incorporating them into insurance plans.

Gene mutations in the EGFR signaling pathway have emerged as a significant aspect of CRC treatment and prognosis, as their alterations may determine the therapeutic response to anti-EGFR receptor therapy. Several studies have demonstrated that patients harboring *RAS* alterations have a much shorter survival than patients with wild-type tumors (24,25). The 37.0% *RAS* mutation frequency observed in this study is similar to that in other Chinese (40.15%) and Asian studies (17,26,27). However, it is lower than that in several Western countries (~50%) (28) but higher than that in patients from the Middle East (19.5%) (29). The discrepancy may be attributed to different diagnostic techniques, ethnicities, genetic factors, multiple sample sizes, and regional diversity. More in-depth investigations are needed to further understand the mechanisms and pathways that might affect mutations in *RAS* genes.

BRAF mutation status is considered a biomarker of poor

prognosis in patients with advanced CRC. Previous analyses have proven that CRC patients with *BRAF* mutations have a lower survival and shorter progression-free survival (PFS) than *BRAF* wild-type patients (30,31). In the current study, *BRAF*-mutated tumors accounted for 9.9% of all patients suffering from advanced CRC, consistent with studies conducted in other countries (8–12%) (32-35). This suggests that from the perspective of *BRAF* genes, the prognosis of patients with CRC in China is similar to that of other countries.

MSI is the only predictive biomarker approved by the FDA for immune checkpoint blockade inhibitor therapy, such as pembrolizumab and nivolumab (36). In this investigation, MSI testing was performed in 30.4% of colon cancer patients and 25.3% of rectal cancer patients, far from the recommendation of the Chinese Society of Clinical Oncology (CSCO) guidelines. Notably, MSI-H mutations were more frequent in the colon (10.6%) than in the rectum (5.6%), which is consistent with previous research findings (37). The reasons affecting MSI-H incidence vary. First, MSI-H prevalence varies by population; for example, in CRC, MSI-H is most common among Egyptians (37%) and African Americans (20–45%) but least common among Europeans and Americans (8–20%). In comparison to MSI-H, the incidence in Chinese patients is approximately 4.5–15%. Second, MSI-H incidence varies among different stages. MSI-H is more common in stage II CRC (20%) than stage III (12%), and it is rare in stage IV (4%) (38). Finally, the incidence was obtained using several approaches or panels composed of varying microsatellite markers. According to a meta-analysis of 17 articles, the incidence of MSI-H in Chinese CRC patients ranged from 7.7% to 13.5% when utilizing various diagnostic methodologies or panels (39).

Some potential limitations need to be addressed in this study. Firstly, most Chinese people preferred to attend tertiary hospitals for CRC treatment since these facilities have the ability and equipment to treat cancer patients holistically. As a result, the catchment of CRC patients was performed at tertiary hospitals in this study. However, a smaller proportion of patients were being treated at lower-grade hospitals. Thus, the current study results cannot be generalized to lower-grade hospitals in China. Secondly, the data quality was partly dependent on the thoroughness of the clinician's records, and it is possible that some biomarker testing information was not included. For example, patients were sometimes treated in multiple hospitals, and it is possible that information concerning biomarker testing was missed.

Conclusions

In conclusion, biomarker testing in advanced CRC patients has become routine in clinical practice in China. However, the rate of biomarker testing was relatively low. The findings of this study underscore the need to eliminate discrepancies in CRC biomarker testing and highlight the limited application of the Chinese guidelines, particularly in regard to MSI testing.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-988/rc

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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. The study was approved by the independent review board of Henan Cancer Hospital (No. 2019273), and all patients provided signed informed consent form. The study was conducted in accordance with the Declaration of Helsinki Declaration (as revised in 2013).

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