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Temporal Change in Treatment Patterns of Metastatic Colorectal Cancer and Its Association with Patient Survival: A Retrospective Cohort Study Based on an Intelligent Big-Data Platform

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ABSTRACT

There is a lack of high-quality, large-scale, real-world evidence from patients with metastatic colorectal cancer (mCRC), especially in China. It remains unclear whether efforts to improve the quality of care for mCRC would improve patient survival outcomes in real-world practice. On the basis of an intelligent big-data platform, we established a large-scale retrospective cohort of mCRC patients. We investigated the temporal changes in the systemic and local treatment (resection, ablation, or radiation to liver, lung, or extrahepatic and/or extrapulmonary metastases) patterns of mCRC, and whether these changes were associated with improved overall survival (OS) over time. Between July 2012 and December 2018, 3403 eligible patients were included in this research. The median OS was 42.8 months (95% confidence interval (CI), 40.7–46.6) for the entire cohort, 25.6 months (95% CI, 24.7–26.9) for those treated with systemic therapy only, and not reached (95% CI, 78.6 months–not reached) for those receiving local therapy. The utility rate of local therapy increased continuously from 37.9% in 2012–2014 to 46.9% in 2017–2018. A dramatic increase in the utility rate of either cetuximab or bevacizumab was observed since 2017 (39.9%, 43.2%, and 60.3% in 2012–2014, 2015–2016, and 2017–2018, respectively). Compared with 2012–2014, the OS of the entire population significantly improved in 2015–2016 (hazard ratio (HR) = 0.87 (95% CI, 0.78–0.99); P = 0.034), but not for patients receiving systemic therapy only (HR = 0.99 (95% CI, 0.86–1.14); P = 0.889), whereas an improved OS was found in 2015–2018 for both the entire population (HR = 0.75 (95% CI, 0.70–0.81); P < 0.001) and for patients receiving systemic therapy only (HR = 0.83 (95% CI, 0.77–0.91); P < 0.001). In summary, the quality of care for mCRC, as indicated by the utility rate of targeted and local therapies, has been continuously improving over time in this study cohort, which is associated with continuously improving survival outcomes for these patients.

1. Introduction

During the period of time in which 5-fluorouracil with leucovorin was the mainstay therapeutic regimen for patients with metastatic colorectal cancer (mCRC), the median overall survival (OS) was stagnant at approximately 8–12 months [1]. With the introduction of oxaliplatin and irinotecan in 2000, the combination regimens 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX) and 5-fluorouracil/leucovorin plus irinotecan (FOLFIRI) became standard therapies in first-line treatment [2]. Moreover, targeted biological therapies that selectively acted on crucial pathways in cancer progression, such as anti-vascular endothelial growth factor

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(VEGF) or anti-epidermal growth factor receptor (EGFR) agents, further improved life expectancy [3–5].

Another advancement in the treatment of mCRC was the increased recognition that surgically resecting liver-limited metastases to achieve no evidence of disease (NED) may possibly achieve long-term survival outcomes [6,7]. Approximately 30%–50% of mCRC patients present with liver metastasis at the time of diagnosis or disease relapse, and 15%–25% of these patients are potential surgical candidates [7–9]. Retrospective studies in patients who underwent R0 hepatectomy suggest five-year OS rates exceeding 50% [10,11]. In addition, there is increased evidence on the use of radiofrequency ablation (RFA) and stereotactic body radiation therapy (SBRT) as reasonable, alternative options for non-surgical candidates and for those with disease recurrence after hepatectomy [12,13]. Moreover, local treatment strategies for mCRC liver metastases have been commonly applied to manage lung metastases [14–16]. Still, there is a lack of causal evidence from randomized studies demonstrating the efficacy of local therapy on colorectal liver or lung metastases, especially in the era of targeted therapy, as randomized trials addressing this issue are neither ethical nor feasible at present.

With the aforementioned improvements in managing mCRC, changing treatment patterns have been observed among patients in North America and some European countries [17,18]. In China, there is a substantial disparity between real-world clinical practice and standard-of-care guidelines for managing patients with mCRC [19]; meanwhile, survival outcomes of mCRC patients are poorer in China than in developed countries [20,21]. However, owing to the lack of high-quality, large-scale, real-world evidence from mCRC patients in China, it remains unclear whether efforts to improve the quality of care for mCRC would improve patient survival and narrow this gap. In this context, we conducted a large-scale retrospective cohort study to investigate temporal changes in the systemic and local treatment patterns for mCRC at Sun Yat-sen University Cancer Center, and to determine whether these changes were associated with improved patient survival outcomes over time.

2. Methods

2.1. Study population and data extraction

This research was a single-institution, retrospective cohort study. Eligible patients were aged 18 or older with histologically confirmed mCRC at Sun Yat-sen University Cancer Center. The detailed patient inclusion and exclusion process is shown in Fig. S1 in Appendix A.

The examined covariates included age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, year of diagnosis, primary tumor location, metastatic site, mutation status of Kirsten rat sarcoma viral oncogene homolog (*Kras*) or neuroblastoma rat sarcoma viral oncogene homolog (*Nras*) exon 2–4 and V600E mutation of the B-type Raf kinase gene ($Braf^{V600E}$), and treatment information on surgery, RFA, SBRT, and systemic therapy. All this information was extracted intelligently from the Big-Data Alliance for Colorectal Cancer (BACC) platform (YiduCloud Technology Ltd., China). The BACC platform is an intelligent big-data platform that integrates and converges large-scale multi-source heterogeneous electronic health-record data from multiple medical centers and hospitals from all over China. On the basis of machine learning and artificial intelligence, the platform structures, normalizes, and integrates information from hospital systems (e.g., admission, discharge, transfer, and surveillance), electronic medical records, and resource information systems including the results of radiological and nuclear imaging, endoscopy, ultrasound, electrocardiography, and pathology and laboratory tests; reorganizes essential data into a table format; and helps in visualizing patients' diagnosis and treatment data along the time axis, thus facilitating routine clinical practice and scientific research.

All patients provided written informed consent for the storage and use of their information in the hospital database. Study approval was obtained from the independent ethics committees at Sun Yat-sen University Cancer Center. The study was undertaken in accordance with the ethical standards of the World Medical Association Declaration of Helsinki.

2.2. Outcome measurement

The outcomes of interest included OS and temporal changes in the utility rate of the following systemic and local therapies: ① cytotoxic agents (i.e., fluoropyrimidines, oxaliplatin, and irinotecan); ② targeted therapies (i.e., cetuximab, bevacizumab, and/or regorafenib); ③ surgical resection, RFA, and/or SBRT to liver, lung, or extrahepatic and/or extrapulmonary metastases; ④ local therapy as the initial course of treatment for mCRC; and ⑤ systemic therapy followed by local therapy. We also assessed the temporal changes in the percentage of patients in whom NED (i.e., elimination or remission of all gross lesions) was achieved after systemic and/or local therapies. Treatment information was collected from the date of initial diagnosis with mCRC to the date of the last visit to the inpatient or outpatient departments at our center. OS was measured from the date of initial diagnosis with mCRC to the date of death from any cause or last follow-up.

2.3. Statistical analysis

The 95% confidence interval (CI) for the utility rate of given therapy was estimated using the Clopper–Pearson method. Survival curves were generated using the Kaplan–Meier method, with comparisons between groups performed using the log-rank test. The association between the variable of interest and OS outcomes was indicated by the hazard ratio (HR) and corresponding 95% CI obtained from the multivariable Cox proportional hazards model adjusted for baseline covariates, including age, sex, performance status, primary tumor location, number of metastatic sites, and molecular subtype.

Statistical significance was set as $P < 0.05$ in a two-tailed test. All statistical analyses were performed using R software version 3.6.1[†].

Descriptive metrics of OS include median OS duration (95% CI) and five-year OS probability (95% CI).

3. Results

3.1. Patient characteristics and treatment exposure

Between July 2012 and December 2018, a total of 3403 eligible mCRC patients were included in the study (Fig. S1). The baseline characteristics of the patients are summarized in Table S1 in Appendix A. The majority of the patients were male, were younger than 65 years old, had moderately impaired performance status, had left-sided tumors, or had liver metastases. Rat sarcoma viral oncogene homolog (*Ras*)/*Braf* mutation status was evident in 34.3% of the patients, the majority of whom had *Ras*-mutated disease.

The median interval between the date of initial diagnosis with mCRC and the date of initial local or systemic treatment for mCRC at our center was 1.0 month (interquartile range, 0.5–3.4). During

[†] http://www.r-project.org

the entire treatment course for mCRC, 43.4% of the patients received local therapy (i.e., surgical resection, RFA, and/or SBRT) to the liver (32.0%), lung (12.1%), or extrahepatic and/or extrapulmonary metastases (7.1%). NED was achieved in 948 patients (27.9% of the entire cohort and 64.2% of those receiving local therapy). For patients who received systemic treatment (n = 2978), the therapeutic agents (utility rates) included fluoropyrimidines (99.2%), oxaliplatin (94.1%), irinotecan (56.7%), bevacizumab (38.5%), cetuximab (17.5%), regorafenib (4.8%), and others (9.3%).

3.2. Survival outcomes with or without local therapy

With a median follow-up of 32.8 months (95% CI, 31.5–33.9), the median OS for the entire cohort was 42.8 months (95% CI, 40.7–46.6; Fig. 1(a)). For patients treated with systemic therapy only, the median OS was 25.6 months (95% CI, 24.7–26.9); for those receiving local therapy, the median OS was not reached (NR) (95% CI, 78.6 months–NR) and the five-year OS probability was 59.8% (95% CI, 56.0%–63.9%). The five-year OS probability was 61.0% (95% CI, 56.9%–65.3%) among patients receiving local therapy limited to liver and/or lung lesions and 53.5% (95% CI, 43.9%–65.3%) among those receiving local therapy to extrahepatic and/or extrapulmonary metastases (Fig. S2 in Appendix A). Moreover, for patients in whom NED was achieved, the five-year OS probability reached 72.8% (95% CI, 68.7%–77.2%; Fig. 1(b)).

3.3. Temporal changes in patterns of systemic and local therapy

To guarantee comparable sample sizes for each group, patients were classified into the following temporal groups according to the year of diagnosis: 2012–2014 (n = 1044), 2015–2016 (n = 1135), and 2017–2018 (n = 1224). Because of the large sample size, statistically significant imbalances between different temporal groups were detected in performance status and molecular subtype; however, the absolute differences were numerically small (Table S2 in Appendix A).

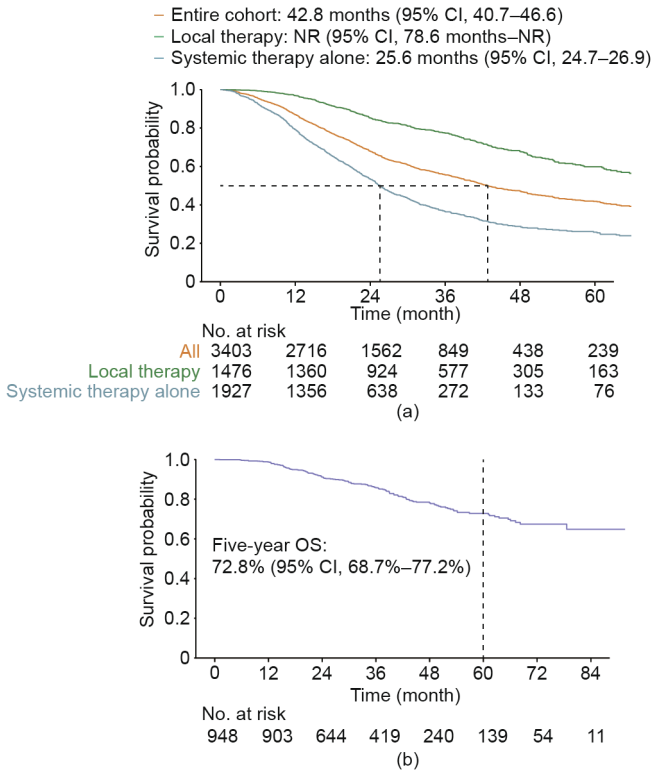

Fig. 1. OS of (a) the entire cohort, patients receiving local therapy, and those receiving systemic therapy only; and (b) patients in whom no evidence of disease was achieved. NR: not reached.

As shown in Fig. 2(a), the percentage of those receiving all three cytotoxic agents (i.e., fluoropyrimidines, oxaliplatin, and irinotecan) during the treatment course was above 50% among all three temporal groups. Notably, the utility rate of either cetuximab or bevacizumab increased modestly from 39.9% (95% CI, 36.7%–43.2%) in 2012–2014 to 43.2% (95% CI, 40.0%–46.4%) in 2015–2016, but then increased dramatically to 60.3% (95% CI, 57.3%–63.2%) in 2017–2018. Similar trends were observed for both cetuximab and bevacizumab. The utility rate of regorafenib also increased continuously over time.

As shown in Fig. 2(b), the utility rate of local therapy increased continuously over time, from 37.9% (95% CI, 35.0%–41.0%) in 2012–2014 to 44.6% (95% CI, 41.7%–47.5%) in 2015–2016 and 46.9% (95% CI, 44.1%–49.7%) in 2017–2018. The utility rate of local therapy to liver metastases showed a consistent pattern of increase over time, whereas the utility rates of local therapy to lung metastases or extrahepatic and/or extrapulmonary metastases were comparable between the time periods. It is notable that the percentage of patients who received local therapy as the initial course of treatment was comparable among the temporal groups; in contrast, the percentage of patients who received systemic therapy followed by local therapy increased continuously from 17.5% (95% CI, 15.3%–20.0%) in 2012–2014 to 21.7% (95% CI, 19.3%–24.2%) in 2015–2016, and further reached 28.2% (95% CI, 25.7%–30.8%) in 2017–2018. More importantly, the percentage of patients in whom NED was achieved also increased continuously over time, from 23.4% (95% CI, 20.8%–26.1%) in 2012–2014 to 26.7% (95% CI, 24.1%–29.4%) in 2015–2016 and 32.8% (95% CI, 30.1%–35.5%) in 2017–2018 (Fig. 2(b)).

3.4. Association between temporal changes in treatment patterns and survival outcomes

In view of the temporal changes in the treatment patterns and median follow-up durations, we further defined the following temporal groups for subsequent survival analyses: ① 2012–2014 (reference group; 65.3 months (95% CI, 63.3–66.7)); ② 2015–2016 (increased utility of local therapy but not targeted therapy; 42.2 months (95% CI, 40.9–42.8)); and ③ 2015–2018 (increased utility of both local therapy and targeted therapy; 27.7 months (95% CI, 27.0–28.7)).

Compared with 2012–2014, the OS was significantly improved in 2015–2016 (42.1 months (95% CI, 37.9–50.0) vs 33.9 months (95% CI, 31.0–38.0); HR = 0.87 (95% CI, 0.78–0.99); P = 0.034; Fig. 3(a)). However, for patients receiving systemic therapy only, the OS did not significantly differ between the two periods (22.9 months (95% CI, 21.1–25.1) vs 24.4 months (95% CI, 22.6–26.1); HR = 0.99 (95% CI, 0.86–1.14); P = 0.889; Fig. 3(b)).

Compared with 2012–2014, the median OS was significantly improved and, strikingly, reached 51.6 months (95% CI, 49.1–NR) in 2015–2018 (HR = 0.75 (95% CI, 0.70–0.81); P < 0.001) as shown in Fig. 4(a). Moreover, for patients treated with systemic therapy only, the OS was still significantly improved in 2015–2018 (26.5 months (95% CI, 25.0–29.3)) compared with 2012–2014 (HR = 0.83 (95% CI, 0.77–0.91); P < 0.001) as shown in Fig. 4(b).

3.5. Subgroup analysis by primary tumor location

As shown in Fig. S3(a) in Appendix A, the temporal increase in the use of cetuximab was largely limited to left-sided tumors, whereas the increase in the use of bevacizumab over time was more prominent in right-sided tumors. Moreover, the increase in the use of local therapy over time was observed in both the

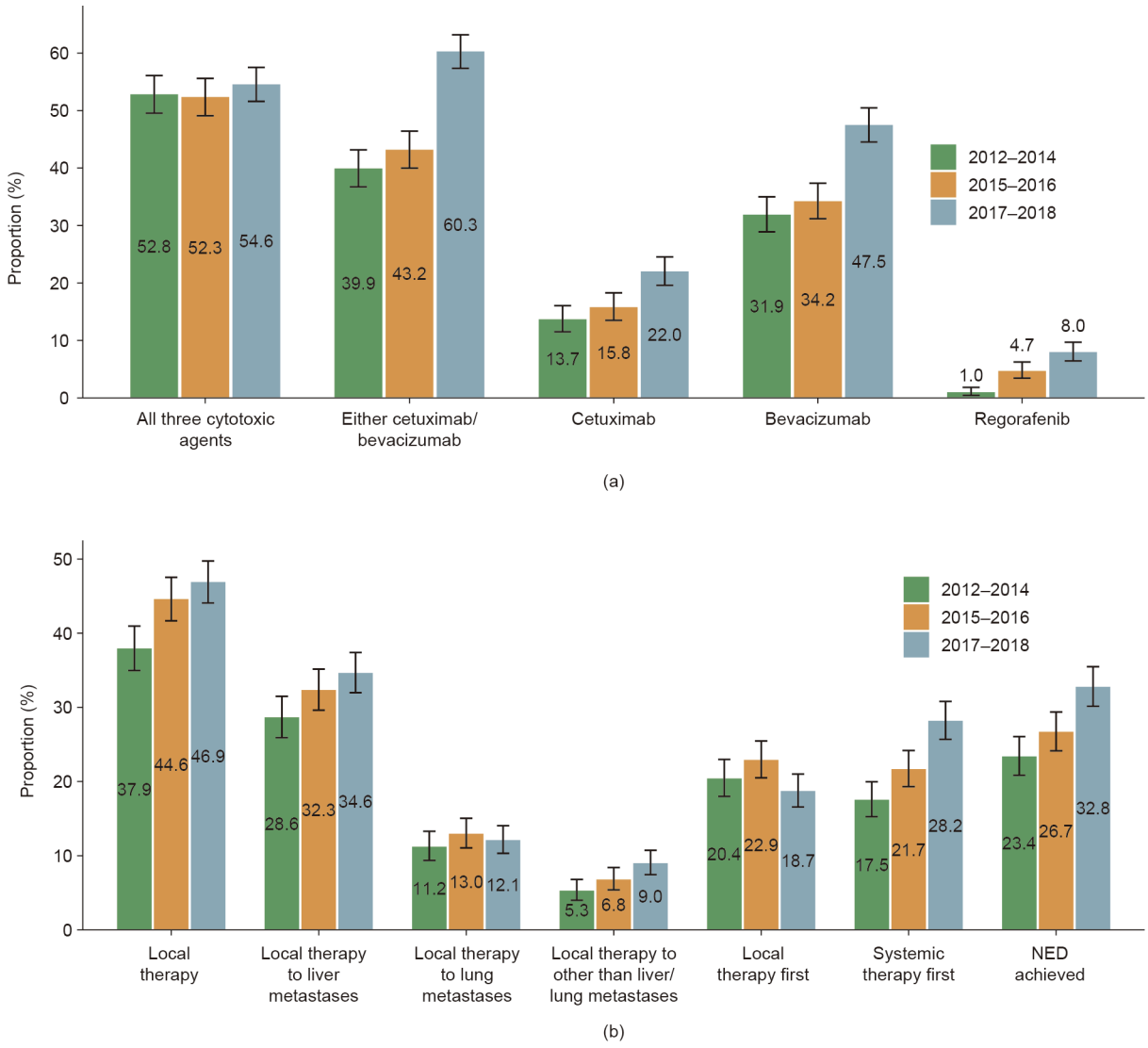

Fig. 2. Temporal changes in (a) systemic treatment and (b) local treatment patterns. To guarantee a comparable sample size for each group, patients were classified into the following temporal groups according to year of diagnosis: 2012–2014 (n = 1044), 2015–2016 (n = 1135), 2017–2018 (n = 1224). Only patients that received systemic therapy (n = 2978) were included in the analysis of temporal changes in systemic treatment patterns.

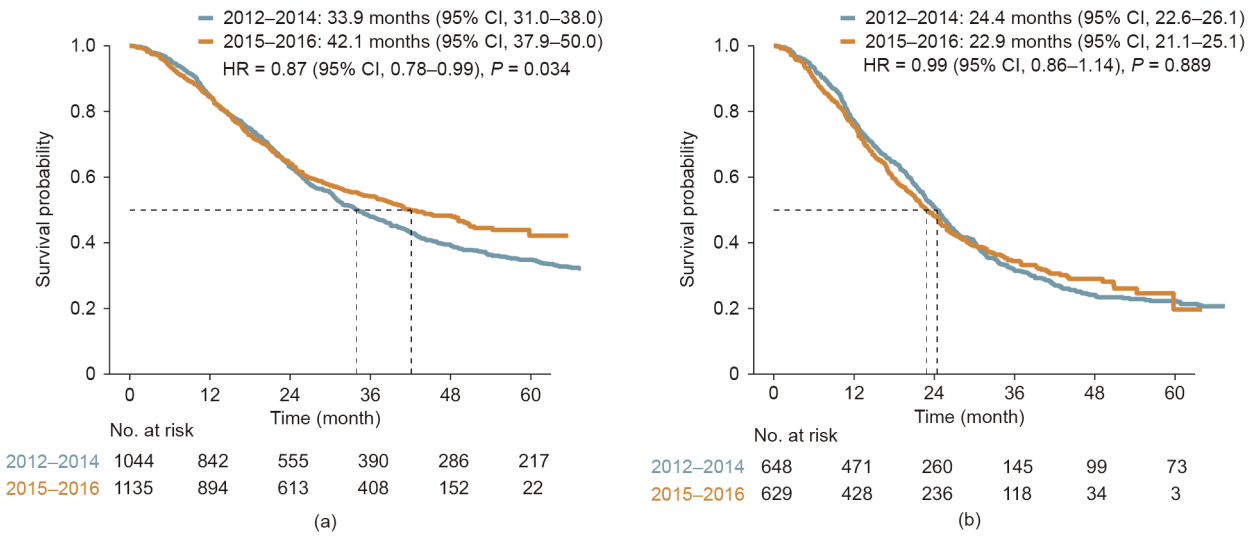

Fig. 3. OS of patients in 2015–2016 versus that of patients in 2012–2014. (a) Entire population; (b) patients that received systemic therapy only.

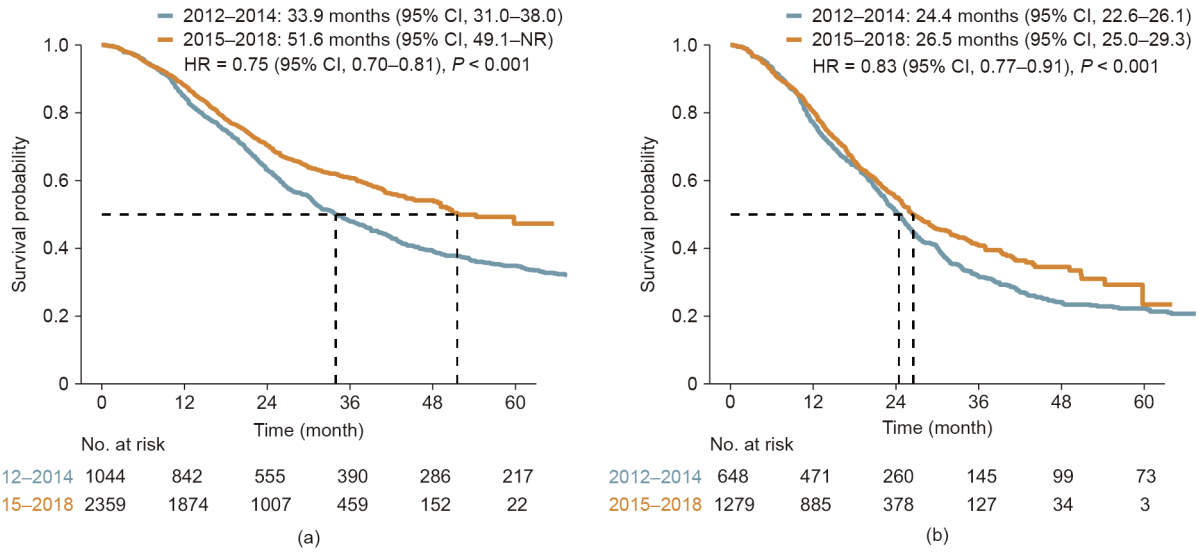

Fig. 4. OS of patients in 2015–2018 versus that of patients in 2012–2014. (a) Entire population; (b) patients that received systemic therapy only.

left- and right-sided subgroups (Fig. S3(b)). In 2012–2014 and 2015–2016, the utility rate of local therapy was higher in patients with left-sided tumors than in those with right-sided tumors; this gap diminished over time, and the utility rate of local therapy was comparable between the left- and right-sided subgroups (approximately 45% for both) in 2017–2018 (Fig. S3(b)).

Overall, patients with right-sided tumors exhibited significantly worse median OS than those with left-sided tumors (37.1 months (95% CI, 31.8–42.1) vs 43.4 months (95% CI, 40.7–48.5); HR = 1.21 (95% CI, 1.06–1.37); $P = 0.005$) as shown in Fig. 5(a). Primary tumor location remained a significant prognostic factor among patients treated with systemic therapy only (21.7 months (95% CI, 19.8–24.2) vs 26.7 months (95% CI, 25.2–29.9); HR = 1.24 (95% CI, 1.07–1.44); $P = 0.005$) as shown in Fig. 5(b), whereas OS was comparable in patients with left-sided tumors and those with right-sided tumors who received local therapy (HR = 0.92 (95% CI, 0.70–1.21); $P = 0.571$) as shown in Fig. 5(c).

4. Discussion

In this study of an mCRC cohort at Sun Yat-sen University Cancer Center, the largest Chinese mCRC cohort thus far with elaborate treatment and outcome information, we demonstrate that the advancements in the treatment of mCRC mainly occurred in two stages, which were coupled with improved survival outcomes. The first stage of improvement was in 2015–2016, with an increased utility rate of local therapy but not targeted therapy. Correspondingly, improved OS was observed for the entire population but not for those receiving systemic therapy only in this period. The second stage of improvement started in 2017, when the utility rate of targeted therapy and that of systemic therapy followed by local therapy substantially increased. Improved OS was also observed for the entire population as well as for those receiving systemic therapy only in 2015–2018. In addition to the observed increase in the utility of local and targeted therapy and multimodality treatment strategies, the improved patient survival may reflect our continuous efforts over the past decade in investigating novel anti-cancer agents and therapeutic strategies and developing clinical practice guidelines and consensus for colorectal cancer (CRC) [22–29].

It is well recognized that only 15%–25% of patients with colorectal liver metastases are eligible for upfront resection [7–9]. Conversion chemotherapy, with or without anti-EGFR or anti-VEGF therapies, has been shown to be capable of converting selected patients to resectability, with the conversion rate varying greatly from 13% to above 40% [30–33]. Moreover, local and conversion treatment strategies for colorectal liver metastases have also been commonly applied to managing lung metastases, albeit with scarce relevant evidence. In this present cohort, the utility rate of local therapy (i.e., surgical resection, RFA, and/or SBRT to the liver, lung, or extrahepatic and/or extrapulmonary metastases) as the initial course of treatment was stagnant at around 20% over time, whereas the utility rate of systemic therapy followed by local therapy continued to increase after 2017, with a 47% utility rate of local therapy in 2017–2018. More importantly, with the advancements in systemic and/or local therapies, the percentage of patients in whom NED was achieved increased continuously over time, exceeding 30% in 2017–2018; the five-year OS probability for such patients reached 73% in our cohort, which was comparable to that of patients with liver-limited metastases receiving R0 hepatectomy [10,11]. Altogether, these findings provide compelling evidence of the value of appropriate local therapy to achieve long-term survival outcomes in selected patients; and highlight the importance of multidisciplinary conferencing and cooperation to determine the optimal multimodality treatment strategies, such as the timing of systemic and local therapy and the choice of systemic therapeutic regimens and local treatment approaches, for mCRC patients.

Over the past decade, there has been mounting evidence of the attenuated efficacy of anti-EGFR therapy in right-sided mCRC compared with left-sided tumors [34–37]. Such data have led the North American National Comprehensive Cancer Network (NCCN) guidelines for CRC to recommend against the use of anti-EGFR agents in the first-line treatment of *ras* wild-type right-sided mCRC since 2017 [38]. Notably, even before this update in the NCCN guidelines, the temporal increase in the use of cetuximab in our cohort was largely limited to those with left-sided tumors, which is reflective of the leading-edge management of mCRC at our institution [39]. Moreover, prior studies have demonstrated that primary tumor location is predictive of survival outcomes for mCRC patients, irrespective of systemic treatment regimens [34,40]. Consistent with these findings, patients with right-sided tumors exhibited significantly worse OS than those with left-sided tumors when treated with systemic therapy only in the current study. Nonetheless, for the patients that received local therapy, OS was comparable

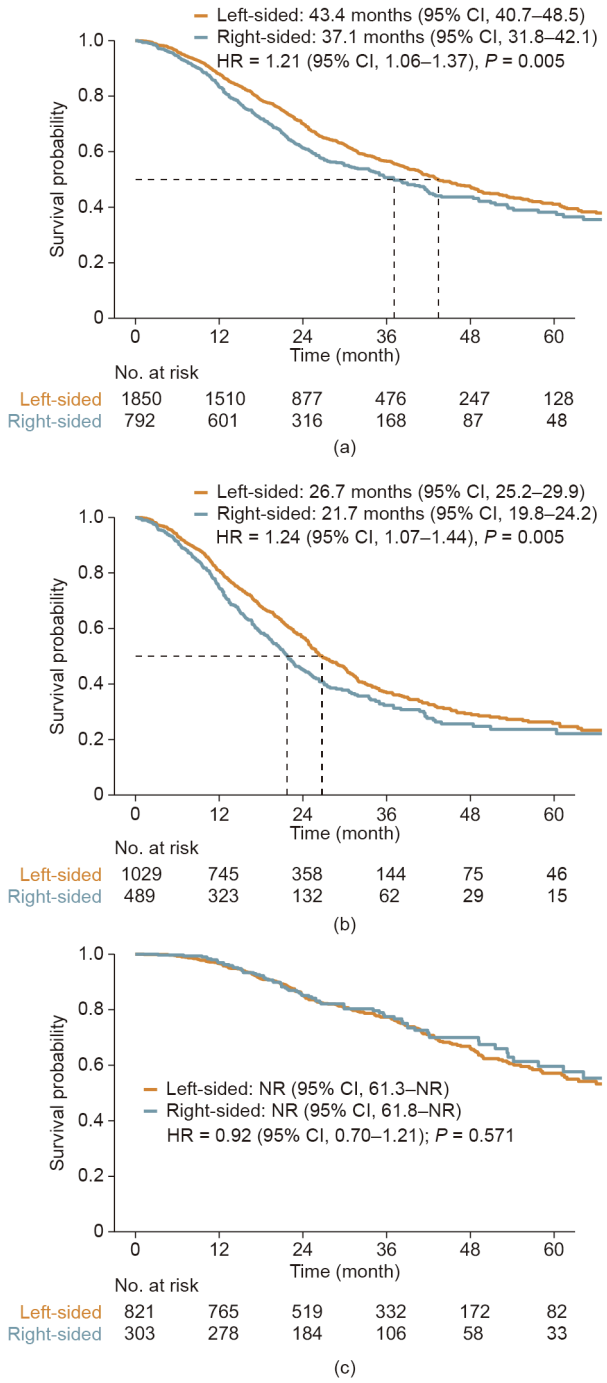

Fig. 5. OS in patients with right-sided tumors versus those with left-sided tumors. (a) Entire population; (b) patients that received systemic therapy only; (c) patients that received local therapy.

between right- and left-sided mCRC patients, which is consistent with previous observations of favorable survival outcomes after curative-intent hepatectomy in patients with right-sided tumors [41,42]. More importantly, although the rate of receiving local therapy was lower in the right-sided subgroup than in the left-sided subgroup before 2017, a similar utility rate of local therapy was achieved in the right- and left-sided subgroups in 2017–2018 (approximately 45% for both), which could be attributed to the improvement in systemic therapeutic regimens and multidisciplinary management.

Although it has been reported that the Asian CRC population may have longer OS than the Caucasian population [43], prior evidence has shown that the survival outcomes of mCRC were much poorer in China compared with developed countries [17,18]. A possible explanation might be the difference in economic status, as the utility rate of cetuximab and bevacizumab in China—even after being included in the national insurance reimbursement list in 2017—was still lower than that in developed countries [24]. Moreover, a recent multi-institutional study suggested a substantial discrepancy between clinical practice and guidelines for managing mCRC patients in China [19]. It is notable that the present study provides encouraging data showing that the median OS for patients with mCRC has reached 43 months at our institution, which is one of the top two cancer centers in China. When examined separately, the survival outcomes for patients receiving local therapy and for those receiving systemic therapy only both compared favorably with those of other international high-volume centers [10,11,44–46]. The percentage of patients receiving all three cytotoxic agents—an indicator of the "continuum of care" that has been associated with prolonged OS [47]—has been greater than 50% at our center since 2012, which is comparable to the percentage in the trial setting [48,49]. Taken together, these findings suggest that in-depth education programs and training courses for oncologists are paramount in improving the nationwide quality of care for mCRC patients, as well as in narrowing the gap between China and developed countries.

Our study has several limitations. First, although imaging information, pathology reports, laboratory tests, and pharmaceutical and surgical records from clinical practice at our center are almost entirely captured by the BACC platform, information on the management of mCRC before patients visited our center can only be extracted from the History of Present Illness records, which can result in substantial amounts of missing data for certain variables (e.g., *Ras*/*Braf* mutation status). Future advancement in machine learning and artificial intelligence techniques for natural language processing and improvement in front-end electronic medical record systems would hopefully mitigate this challenge. Second, although the BACC platform now covers more than 25 hospitals in China, only the processed data from our center are mature enough for elaborate analyses at present. Future multi-center cohort studies based on this platform are warranted to further assess the generalizability of our findings in other institutions in China. Third, although our time-trend analysis avoids selection bias from retrospectively comparing survival outcomes in patients with or without targeted or local therapy, there might exist some unobserved covariates that were imbalanced between the temporal groups, which may have introduced potential bias to our findings.

5. Conclusions

This study demonstrates that the clinical management of mCRC patients, as indicated by the utility rate of targeted and local therapies, has been continuously evolving at Sun Yat-sen University Cancer Center, and is associated with continuously improving patient survival outcomes. Our findings document the rationale for promoting multidisciplinary conferencing and cooperation and refining multimodality treatment approaches, as well as providing in-depth education and training for oncologists, in order to improve the nationwide quality of care for managing mCRC patients in China.

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Compliance with ethics guidelines

Zi-Xian Wang, Yi-Chen Yao, Zong-Jiong Mai, Wu-Hao Lin, You-Sheng Huang, Ying Jin, Hui-Yan Luo, Dong-Sheng Zhang, Feng-Hua Wang, Feng Wang, Gong Chen, Pei-Rong Ding, Yun-Fei Yuan, Yu-Hong Li, Jin-Hua Huang, Zhi-Zhong Pan, and Rui-Hua Xu declare that they have no conflict of interest or financial conflicts to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eng.2020.10.017.

References

[1] Piedbois P, Rougier P, Buyse M, Pignon J, Ryan L, Hansen R, et al.; Meta-analysis Group in Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. J Clin Oncol 1998;16(1):301–8.
[2] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines®): colon cancer [Internet]. Plymouth Meeting: National Comprehensive Cancer Network; [cited 2020 Jan 17]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
[3] Douillard JY, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, et al. Panitumumab-FOLFOX4 treatment and *RAS* mutations in colorectal cancer. N Engl J Med 2013;369(11):1023–34.
[4] Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009;360(14):1408–17.
[5] Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008;26(12):2013–9.
[6] Raoof M, Haye S, Ituarte PHG, Fong Y. Liver resection improves survival in colorectal cancer patients: causal-effects from population-level instrumental variable analysis. Ann Surg 2019;270(4):692–700.
[7] Kopetz S, Chang GJ, Overman MJ, Eng C, Sargent DJ, Larson DW, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol 2009;27(22):3677–83.
[8] Vera R, González-Flores E, Rubio C, Urbano J, Valero Camps M, Ciampi-Dopazo JJ, et al. Multidisciplinary management of liver metastases in patients with colorectal cancer: a consensus of SEOM, AEC, SEOR, SERVEI, and SEMNIM. Clin Transl Oncol 2020;22(5):647–62.
[9] Chow FL, Chok KH. Colorectal liver metastases: an update on multidisciplinary approach. World J Hepatol 2019;11(2):150–72.
[10] Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol 2007;25(29):4575–80.
[11] Hur H, Ko YT, Min BS, Kim KS, Choi JS, Sohn SK, et al. Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver metastases. Am J Surg 2009;197(6):728–36.
[12] Sucandy I, Cheek S, Golas BJ, Tsung A, Geller DA, Marsh JW. Longterm survival outcomes of patients undergoing treatment with radiofrequency ablation for hepatocellular carcinoma and metastatic colorectal cancer liver tumors. HPB 2016;18(9):756–63.
[13] Rusthoven KE, Kavanagh BD, Cardenes H, Stieber VW, Burri SH, Feigenberg SJ, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. J Clin Oncol 2009;27(10):1572–8.
[14] Åberg T, Malmberg KÅ, Nilsson B, Nõu E. The effect of metastasectomy: fact or fiction? Ann Thorac Surg 1980;30(4):378–84.
[15] Gonzalez M, Poncet A, Combescure C, Robert J, Ris HB, Gervaz P. Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis. Ann Surg Oncol 2013;20(2):572–9.
[16] Gonzalez M, Gervaz P. Risk factors for survival after lung metastasectomy in colorectal cancer patients: systematic review and meta-analysis. Future Oncol 2015;11(2S):31–3.
[17] Abrams TA, Meyer G, Schrag D, Meyerhardt JA, Moloney J, Fuchs CS. Chemotherapy usage patterns in a US-wide cohort of patients with metastatic colorectal cancer. J Natl Cancer Inst 2014;106(2):djt371.
[18] McLean J, Rho YS, Kuruba G, Mamo A, Gilabert M, Kavan T, et al. Clinical practice patterns in chemotherapeutic treatment regimens for metastatic colorectal cancer. Clin Colorectal Cancer 2016;15(2):135–40.
[19] Xu R, Wang W, Zhu Bo, Lin X, Ma D, Zhu L, et al. Disease characteristics and treatment patterns of Chinese patients with metastatic colorectal cancer: a retrospective study using medical records from China. BMC Cancer 2020;20(1):131.
[20] Qin S, Li J, Wang L, Xu J, Cheng Y, Bai Y, et al. Efficacy and tolerability of first-line cetuximab plus leucovorin, fluorouracil, and oxaliplatin (FOLFOX-4) versus FOLFOX-4 in patients with *RAS* wild-type metastatic colorectal cancer: the open-label, randomized, phase III TAILOR trial. J Clin Oncol 2018;36(30):3031–9.
[21] Zeng H, Chen W, Zheng R, Zhang S, Ji JS, Zou X, et al. Changing cancer survival in China during 2003–15: a pooled analysis of 17 population-based cancer registries. Lancet Glob Health 2018;6(5):e555–67.
[22] Guan ZZ, Xu JM, Luo RC, Feng FY, Wang LW, Shen L, et al. Efficacy and safety of bevacizumab plus chemotherapy in Chinese patients with metastatic colorectal cancer: a randomized phase III ARTIST trial. Chin J Cancer 2011;30(10):682–9.
[23] Luo HY, Li YH, Wang W, Wang ZQ, Yuan X, Ma D, et al. Single-agent capecitabine as maintenance therapy after induction of XELOX (or FOLFOX) in first-line treatment of metastatic colorectal cancer: randomized clinical trial of efficacy and safety. Ann Oncol 2016;27(6):1074–81.
[24] Xu RH, Muro K, Morita S, Iwasa S, Han SW, Wang W, et al. Modified XELIRI (capecitabine plus irinotecan) versus FOLFIRI (leucovorin, fluorouracil, and irinotecan), both either with or without bevacizumab, as second-line therapy for metastatic colorectal cancer (AXEPT): a multicentre, open-label, randomised, non-inferiority, phase 3 trial. Lancet Oncol 2018;19(5):660–71.
[25] Li J, Qin S, Xu R, Yau TCC, Ma B, Pan H, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2015;16(6):619–29.
[26] Xu RH, Li J, Bai Y, Xu J, Liu T, Shen L, et al. Safety and efficacy of fruquintinib in patients with previously treated metastatic colorectal cancer: a phase Ib study and a randomized double-blind phase II study. J Hematol Oncol 2017;10(1):22.
[27] Li J, Qin S, Xu RH, Shen L, Xu J, Bai Y, et al. Effect of fruquintinib vs placebo on overall survival in patients with previously treated metastatic colorectal cancer: the FRESCO randomized clinical trial. JAMA 2018;319(24):2486–96.
[28] Peng J, Li W, Zhang R, Lin J, Tang J, Wen Y, et al. Safety and efficacy of a modified XELOX adjuvant regimen for patients with operated stage III colon cancer: a Chinese single-center experience. Cancer Commun 2019;39(1):59.
[29] Wang F, Wang ZX, Chen G, Luo HY, Zhang DS, Qiu MZ, et al. Expert opinions on immunotherapy for patients with colorectal cancer. Cancer Commun 2020;40(10):467–72.
[30] Adam R, Avisar E, Ariche A, Giachetti S, Azoulay D, Castaing D, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. Ann Surg Oncol 2001;8(4):347–53.
[31] Kataoka K, Kanazawa A, Iwamoto S, Kato T, Nakajima A, Arimoto A. Does, "conversion chemotherapy" really improve survival in metastatic colorectal cancer patients with liver-limited disease? World J Surg 2014;38(4):936–46.
[32] Folprecht G, Gruenberger T, Bechstein WO, Raab HR, Lordick F, Hartmann JT, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol 2010;11(1):38–47.
[33] Garufi C, Torsello A, Tumolo S, Ettorre GM, Zeuli M, Campanella C, et al. Cetuximab plus chronomodulated irinotecan, 5-fluorouracil, leucovorin and oxaliplatin as neoadjuvant chemotherapy in colorectal liver metastases: POCHER trial. Br J Cancer 2010;103(10):1542–7.
[34] Tejpar S, Stintzing S, Ciardiello F, Tabernero J, van Cutsem E, Beier F, et al. Prognostic and predictive relevance of primary tumor location in patients with *RAS* wild-type metastatic colorectal cancer: retrospective analyses of the CRYSTAL and FIRE-3 trials. JAMA Oncol 2017;3(2):194–201.
[35] Venook AP, Niedzwiecki D, Innocenti F, Fruth B, Greene C, O'Neil BH, et al. Impact of primary (1°) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): analysis of CALGB/SWOG 80405 (Alliance). J Clin Oncol 2016;34(Suppl 15):3504.
[36] Arnold D, Lueza B, Douillard JY, Peeters M, Lenz HJ, Venook A, et al. Prognostic and predictive value of primary tumour side in patients with *RAS* wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Ann Oncol 2017;28(8):1713–29.
[37] Wang ZX, Wu HX, He MM, Wang YN, Luo HY, Ding PR, et al. Chemotherapy with or without anti-EGFR agents in left- and right-sided metastatic colorectal cancer: an updated meta-analysis. J Natl Compr Canc Netw 2019;17(7):805–11.
[38] Messersmith WA. Systemic management of colorectal cancer. J Natl Compr Canc Netw 2017;15(5S):699–702.
[39] Wang F, Bai L, Liu TS, Yu YY, He MM, Liu KY, et al. Right-sided colon cancer and left-sided colorectal cancers respond differently to cetuximab. Chin J Cancer 2015;34(9):384–93.
[40] Holch JW, Ricard I, Stintzing S, Modest DP, Heinemann V. The relevance of primary tumour location in patients with metastatic colorectal cancer: a meta-analysis of first-line clinical trials. Eur J Cancer 2017;70:87–98.

[41] Sasaki K, Andreatos N, Margonis GA, He J, Weiss M, Johnston F, et al. The prognostic implications of primary colorectal tumor location on recurrence and overall survival in patients undergoing resection for colorectal liver metastasis. J Surg Oncol 2016;114(7):803–9.
[42] Creasy JM, Sadot E, Koerkamp BG, Chou JF, Gonen M, Kemeny NE, et al. The impact of primary tumor location on long-term survival in patients undergoing hepatic resection for metastatic colon cancer. Ann Surg Oncol 2018;25(2):431–8.
[43] Le H, Ziogas A, Taylor TH, Lipkin SM, Zell JA. Survival of distinct Asian groups among colorectal cancer cases in California. Cancer 2009;115(2):259–70.
[44] Venook AP, Niedzwiecki D, Lenz HJ, Innocenti F, Fruth B, Meyerhardt JA, et al. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type advanced or metastatic colorectal cancer: a randomized clinical trial. JAMA 2017;317(23):2392–401.
[45] Stintzing S, Modest DP, Rossius L, Lerch MM, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final *RAS* wild-type subgroup of this randomised open-label phase 3 trial. Lancet Oncol 2016;17(10):1426–34.
[46] Loupakis F, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L, et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N Engl J Med 2014;371(17):1609–18.
[47] Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol 2004;22(7):1209–14.
[48] Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004;22(2):229–37.
[49] Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, et al. 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(10):1065–75.