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Third-line treatment patterns and clinical outcomes for metastatic colorectal cancer: a retrospective real-world study

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Abstract

Background: There are multiple recommendations on the third-line therapy of metastatic colorectal cancer (mCRC); however, no consensus has been reached.

Objectives: This study aimed to explore the patient demographics and the real-world third-line treatment landscape of mCRC.

Design: A retrospective real-world cohort study.

Methods: Electronic medical records of mCRC patients from Tianjin Medical University Cancer Institute and Hospital between 2013 and 2020 were collected. Upon descriptive, comparative, and survival analyses, a retrospective study was conducted to describe demographics and clinical outcomes of mCRC patients receiving third-line treatment.

Results: Among 218 mCRC patients receiving third-line therapy, 65.5% received chemotherapy combined with or without targeted drugs, followed by anti-angiogenic monotherapy (18.4%), anti-epidermal growth factor receptor drugs (6.9%) and immunotherapy (6.4%). The overall response rate and disease control rate reached 10.2% and 59.2%, respectively; and median progression-free survival (PFS) and overall survival were 4.0 m and 10.7 m, respectively. After Cox multivariate analysis, we found that therapeutic regime was an independent prognostic factor. Compared to patients receiving anti-angiogenic monotherapy, those receiving chemotherapy combined with or without targeted drugs exhibited better prognosis. For patients whose PFS were longer in the front-line treatment, the PFS of third-line therapy was also relatively longer ($p = 0.023$). Multiple types of therapies (>3, $p = 0.002$) or multiple drugs (>5, $p = 0.024$) in the whole-course management of mCRC are indicators of longer survival.

Conclusion: Chemotherapy combined with or without targeted therapy remained dominated third-line choice and showed favorable efficacy compared with anti-angiogenic monotherapy. With the application of more types and quantities of effective drugs, patients would achieve better survival.

Keywords: clinical outcomes, colorectal cancer, real-world evidence, third-line therapy, treatment patterns

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Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed tumors and the second contributor to cancer-related mortality worldwide.[1] The latest progress in the multidisciplinary treatment has greatly improved the survival rate, but most patients with metastatic CRC (mCRC) are still incurable. Clinical factors such as the primary

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tumor location, and molecular markers including the RAS/RAF status influence the choice of first-line treatment in mCRC.[2] Typical first-line or second-line chemotherapy options for mCRC patients include fluorouracil, folic acid and oxaliplatin (FOLFOX) and fluorouracil, folic acid and irinotecan (FOLFIRI).[3,4] Targeted therapies, such as anti-angiogenic agents[5–8] and anti-epidermal growth factor receptor (EGFR) drugs,[9–11] have further improved the efficacy of existing cytotoxic therapies. For those with BRAF-mutant tumors or with an urgent need for cytoreduction, a triplet chemotherapy with fluorouracil, folic acid, oxaliplatin, and irinotecan (FOLFOXIRI) plus bevacizumab may be a reasonable choice in fit patients.[12,13] With the amazing results of KEYNOTE-177, immunotherapy has also been approved for the first-line treatment of dMMR/MSI-H mCRC.[14,15]

With regard to the third-line treatment of mCRC, either regorafenib[16] or the antimetabolite trifluridine/tipiracil (TAS-102)[17] is recommended in patients irrespective of mutation status. Cetuximab or panitumumab, preferably in combination with irinotecan, is also alternative in KRAS/NRAS/BRAF wild-type patients. Even if anti-EGFR agents have been given in the front-line therapy, screened patients can still benefit from anti-EGFR rechallenge strategy in the later-line therapy.[18] The explosion in molecular profiling of tumors has resulted in identification of new targets and combination therapies. Among these, HER2 amplification has emerged as a promising therapeutic target for mCRC. The efficacy of a HER2-directed therapy has been confirmed in clinical trials such as MyPathway[19] and HERACLES.[20] In addition, immunotherapy is increasingly used to treat tumors with dMMR/MSI-H including the third-line treatment of dMMR/MSI-H mCRC. Based on the synergistic effect of immunotherapy and anti-angiogenic therapy, studies exploring the efficacy of programmed cell death protein 1 antibodies combined with anti-angiogenic tyrosine kinase inhibitor provide an alternative treatment option for pMMR/MSS mCRC patients.[21,22]

Based on the guidelines of mCRC, there are a variety of treatment approaches in the third-line setting, but comparative trials evaluating one option against another are lacking. Hence, clinicians will comprehensively determine suitable third-line management strategy depending on the molecular characteristics of the tumor, previous treatment, residual toxicity, accessible drugs, and clinical trial opportunities. In a real-world study from Australia, the choice of third-line treatment varies according to KRAS status and novel drugs availability in clinical trials.[23] In this Australian cohort, the majority of patients chose chemotherapy as their third-line therapy, and 83% of them were given as chemotherapy rechallenge.[23] Another Japanese retrospective study also showed that chemotherapy rechallenge was a valuable option and was more effective than regorafenib in the third-line setting for mCRC patients.[24] For the real-world treatment patterns of Chinese patients with mCRC, the most common sequence from first-line to second-line was from FOLFOX or other oxaliplatin-based regimens to FOLFIRI or other irinotecan-based schemes.[25] However, there was limited available option and no consensus on the choice of third-line therapy at that time in China.[25]

To further explore the patient demographics and the real-world third-line treatment landscape of mCRC, we designed this retrospective study.

Patients and methods

Study design and patients

This retrospective cohort study aimed to assess the real-world third-line treatment patterns and clinical outcomes for mCRC. Patients were carefully selected according to the following inclusion and exclusion criteria. The inclusion criteria were as follows: pathologic diagnosis confirming colorectal adenocarcinoma; metastatic, unresectable CRC; had received third-line treatment with prescription records; available follow-up. If one of the following events occurred, the patients were removed from the study; had other malignancy during the baseline period (with the exception of basal cell carcinoma of the skin and *in situ* cancer of the cervix); development of a second primary cancer during the follow-up period.

Consecutive patients with mCRC receiving third-line treatment from Tianjin Medical University Cancer Institute and Hospital between January 2013 and December 2020 were included. Their demographic data, clinicopathological information, treatment records, imaging examination

results, and survival outcomes were collected in detail from electronic medical records.

Outcomes measures

The date of third-line treatment initiation were defined as the index date. The follow-up period began at the date of third-line treatment initiation and ended at the data cut-off date, last clinic visits date, or death. The baseline clinical characteristics were assessed before or at the index date of third-line treatment initiation. Lines of therapy after mCRC diagnosis were identified using the following definitions based on chemotherapy and/or targeted drugs administrations. The start of first-line therapy was identified as the first administration of chemotherapy or targeted agents after the diagnosis of mCRC. The first-line treatment contained all drugs that were used within 28 days of the start of the regimen. Subsequent lines of treatment were defined as the first administration of any anti-tumor drug not prescribed in the previous line of therapy. Similarly, the subsequent regimens included all anti-tumor drugs administered within 28 days of the first use in that line of therapy. If the treatment interval within a given line of therapy is more than 120 days, the latter treatment was considered as a new line of treatment. The drugs and cycles of each line of therapy were collected in detail.

Outcomes data of third-line therapy, including tumor response results and survival information, were also recorded and assessed. Objective tumor response was based on the data available in the electronic medical records and was further classified as complete response (CR), partial response (PR), stable disease (SD), and disease progression (PD). Overall response rate (ORR) was determined as the rate of a best overall response of CR or PR in patients with measurable lesions at baseline. The date of last follow-up was recorded as censored data for the survival analysis when the time of death or progression could not be confirmed or if the patient was still alive. Progression-free survival (PFS) was defined as the period from the date of treatment to the date of confirmed progression or death from any cause (whichever occurred first) or last contact (for censored patients). PFS1, PFS2, and PFS3 represented PFS of first-line, second-line, and third-line treatments, respectively. Overall survival (OS) was calculated from the date of first-line treatment to the date of death from any cause or last contact (for censored patients), and OS3 was regarded as the time from third-line therapy initiation to death or last contact (for censored patients).

Statistical analysis

All statistical analyses in this study were performed using the IBM SPSS Statistics, Version 20.0 (New York, America). Categorical variables were summarized by percentages and compared using the χ^2 test or the Fisher's exact test. Continuous variables were described by mean, median, standard deviation, and interquartile ranges (or minimum and maximum). OS and PFS were analyzed using the Kaplan–Meier method and were compared using the log-rank test. The 6-, 12-, and 18-month survival rates were calculated from the according survival curves. Furthermore, the univariate and multivariate Cox proportional hazard regression model were used to analyze the potential risk characteristics. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated to quantify the strength of these associations. A p value of <0.05 was considered to be statistically significant, and all statistical tests were two-tailed.

Results

Baseline patient and clinical characteristics

Between January 2013 and December 2020, 218 patients with mCRC who met eligibility criteria were identified from Tianjin Medical University Cancer Institute and Hospital. The baseline patient and disease characteristics at the index date of third-line treatment were listed in Table 1.

The median age at third-line treatment initiation was 58 years. The majority of patients were male (56.9%). Sigmoid colon was the most common tumor location (40.4%), followed by rectum (22.9%) and ascending colon (22.5%). Adenocarcinoma accounts for the majority (72.0%), and only 7.8% of patients were classified as mucinous adenocarcinoma. Most patients with available data for disease stage at initial diagnosis had confirmed stage IV disease (56.9%). Only 42.2% (92/218) of patients received radical resection at the initial treatment. Among them, 79.3% (73/92) of CRC patients received adjuvant chemotherapy, and

Table 1. Baseline patient and disease characteristics (baseline characteristics were assessed at the index date of third-line treatment).

Characteristics	Number	%
Age (years)		
Median (range)	58 (20–84)	
Gender		
Male	124	56.9
Female	94	43.1
Location of primary tumor		
Ascending colon	49	22.5
Transverse colon	14	6.4
Descending colon	11	5.0
Sigmoid colon	88	40.4
Rectum	50	22.9
Unknown	6	2.8
Pathologic differentiation		
Adenocarcinoma	157	72.0
Well differentiated	11	5.0
Moderately differentiated	108	49.5
Poorly differentiated	38	17.5
Mucinous adenocarcinoma	17	7.8
Unknown	44	20.2
Stage at initial diagnosis		
I	5	2.3
II	7	3.2
III	69	31.7
IV	124	56.9
Unknown	13	5.9
Resection of primary tumor		
Radical resection	92	42.2
Palliative resection	86	39.4
None	40	18.4
Adjuvant chemotherapy		
Yes	73	33.5
No	145	66.5
Cycles of adjuvant chemotherapy		
Median (range)	6 (1–12)	
First-line treatment		
Chemotherapy only	133	61.0
Chemotherapy plus targeted drugs	67	30.7
Unknown	18	8.3
First-line targeted drugs		
Anti-VEGF drugs	50	22.9
Anti-EGFR drugs	17	7.8
None	151	69.3
Cycles of first-line treatment		
Median (range)	7 (1–18)	
Second-line treatment		
Chemotherapy only	101	46.3
Targeted drugs only	6	2.8
Chemotherapy plus targeted drugs	105	48.2
Immunotherapy combination	4	1.8
Unknown	2	0.9
Second-line targeted drugs		
Anti-VEGF drugs	102	46.8
Anti-EGFR drugs	13	6.0
None	103	47.2
Cycles of second-line treatment		
Median (range)	6 (1–22)	

(Continued)

Table 1. (Continued)

Characteristics	Number	%
Previous use of targeted drugs		
Anti-VEGF + Anti-EGFR	15	6.9
Anti-VEGF in first-line or second-line treatment	65	29.8
Anti-VEGF in first-line and second-line treatment	37	17.0
Anti-EGFR in first-line or second-line treatment	12	5.5
None	89	40.8
Number of metastatic organs at third-line treatment		
1	117	53.7
2	44	20.2
⩾3	56	25.7
Unknown	1	0.4
Liver-limited metastases at third-line treatment		
Yes	71	32.6
No	147	67.4
Lung-limited metastases at third-line treatment		
Yes	20	9.2
No	198	90.8
Metastatic sites at third-line treatment		
Liver	135	61.9
Lung	67	30.7
Lymph nodes	30	13.8
Peritoneum	33	15.1
Bone	11	5.0
Ovary	14	6.4
Others	36	16.5

EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

the most frequently used regimens (86.3%, 63/73) were the combination of oxaliplatin with fluoropyrimidine.

Front-line treatment characteristics

Among the 218 patients receiving active therapy after tumor recurrence or metastasis, the most frequently used chemotherapy regimens in the first-line therapy were oxaliplatin- and fluoropyrimidine-based therapies (69.3% and 88.5% of patients, respectively) [Figure 1(a)]; FOLFOX and XELOX (capecitabine and oxaliplatin) were the most dominant individual regimen [39.4% (86/218) and 28.4% (62/218) of patients, respectively]. Among patients receiving first-line therapy, chemotherapy alone was most commonly used (61.0%), and 30.7% of them received a combination of chemotherapy and targeted therapies. Most patients chose anti-angiogenic drugs (22.9%) in the first-line combination strategy. The median PFS1 was 8.4 m (range: 1.3–68.0 m), 8.0 m (range: 1.3–68.0 m), and 9.4 m (range: 1.5–44.0 m) in all patients, patients receiving chemotherapy alone, and patients receiving the combination of chemotherapy and targeted drugs, respectively.

In the second-line setting, the most common chemotherapy regimens used were irinotecan-, oxaliplatin-, and fluoropyrimidine-based (72.5%, 22.0%, and 92.7% of patients, respectively) [Figure 1(b)]. The most frequently used individual chemotherapy regimen was irinotecan plus fluoropyrimidine (70.6% of patients). About 52.7% of patients received targeted therapy in their second-line treatment. Among them, 48.2% of patients chose to use it in combination with chemotherapy, and the remaining patients chose targeted therapy alone or in combination with immunotherapy for physical or other reasons. In accordance with the first-line treatment, anti-angiogenic therapy was still the dominated targeted drug choice (46.8%) in the second-line setting. The median PFS2 was 6.0 m (range: 1.0–28.0 m), 5.0 m (range: 1.0–24.0 m), and 7.0 m (range: 1.0–28.0 m) in all patients, patients receiving chemotherapy alone, and patients receiving the combination of chemotherapy and targeted drugs, respectively.

For the application of targeted drugs in front-line treatment, 40.8% of patients did not choose any targeted drugs (Table 1). More than half of

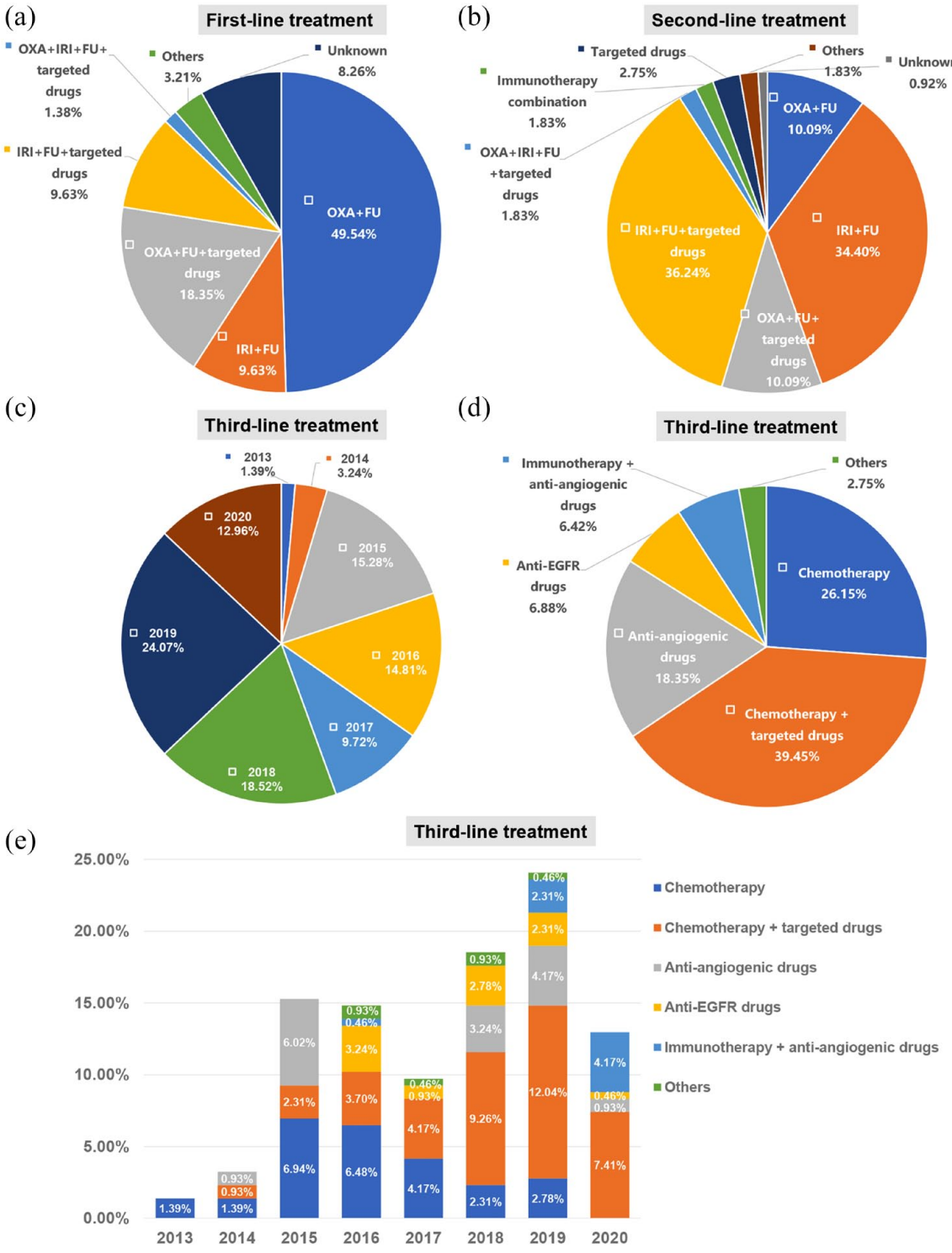

Figure 1. The distribution of treatment patterns of mCRC patients. (a) The first-line treatment patterns. (b) The second-line treatment patterns. (c) The years of patients receiving third-line treatment. (d) The third-line treatment patterns. (e) The distribution of third-line treatment in different years.
FU, fluoropyrimidine; IRI, irinotecan; mCRC, metastatic colorectal cancer; OXA, oxaliplatin.

patients (52.3%) received a single type of targeted agents, and 17% of them used bevacizumab across lines. A total of 15 patients (6.9%) were given sequential prescription of anti-VEGF and anti-EGFR drugs.

Third-line treatment patterns

At the initiation of third-line treatment in our cohort, most patients' metastases were still limited to a single organ (53.7%) (Table 1). The most common metastatic lesions involved the liver (61.9%), followed by lymph nodes (30.7%), peritoneum (15.1%), lung (13.8%), ovary (6.4%), bone (5.0%), and so on.

Among all patients receiving third-line treatment, less than 5% of them were treated in 2013 and 2014 [Figure 1(c)]. But more than 60% of patients were given third-line treatment by the end of 2018 [Table 2 and Figure 1(c)], indicating that with the progress of anti-tumor treatment, more and more patients with mCRC have the opportunity to receive third-line or later-line therapies. In our cohort, the median treatment duration was 4 cycles (range, 1–43). The majority of patients received chemotherapy (65.5%, including traditional oxaliplatin or irinotecan-based chemotherapy (55.5%) and other drugs in clinical research (10.0%) such as raltitrexed or gemcitabine) in their third-line setting, followed by anti-angiogenic monotherapy (18.4%), anti-EGFR drugs (6.9%), and immunotherapy (6.4%) [Table 2 and Figure 1(d)]. The remaining patients (2.8%) received mammalian target of rapamycin (mTOR) inhibitors, anti-HER-2 therapy, or enrolled in new drug clinical trials according to their tumor gene variation results.

The total number of patients receiving active therapy each year since 2013 and the proportion of patients receiving chemotherapy, targeted therapies, or immunotherapies over the same time frame are presented in Figure 1(e). The total number of patients receiving active treatment appeared to be increasing over time. It was shown that the vast majority of patients received chemotherapy combined with or without targeted therapy in the third-line scheme no matter in which year. Among them, 65% of patients were given chemotherapy rechallenge, whereas 35% of them chose new chemotherapeutic drugs, such as gemcitabine, raltitrexed, oxaliplatin, and irinotecan, which had not been used in the front-line treatment. Based on the essential role of anti-angiogenesis therapy in the treatment of mCRC, more than half of patients (53.2%) still received anti-angiogenic drugs in their third-line treatment. With the report of REGONIVO results,[22] it was obvious that the prescription rate of immunotherapy combined with anti-angiogenic drugs had increased in recent years [Figure 1(e)]. Since the development of novel anti-tumor drugs is the backbone of the progress of later-line treatment, nearly 20% of patients in our data were enrolled in the third-line clinical trials, such as those on new anti-angiogenic tyrosine kinase inhibitors or immune checkpoint inhibitors. Treatment was discontinued in a total of 198 (90.8%) of 218 patients because of disease progression. And more than one-third of patients (34.9%) received forth-line or later-line treatment.

Tumor response assessment

In our study, tumor response assessment results of patients receiving third-line treatment were obtained in 206 (94.5%, 206/218) cases. Among them, no patient reached CR, and 21 patients (10.2%, 21/206) achieved PR. The ORR and disease control rate (DCR) reached 10.2% and 59.2%, respectively.

As shown in Table 3, different third-line schemes led to distinct ORR (range: 2.6–42.9%). In patients who had not received anti-EGFR drugs in front-line treatment, whereas chose anti-EGFR monotherapy in their third-line setting, the ORR reached 42.9%, indicating that Rat sarcoma (RAS)/Raf proto-oncogene (RAF)-wild type patients can benefit from anti-EGFR therapies even though it is the first application in the later-line treatment. In recent years, the efficacy of the combination of immunotherapy with anti-angiogenic therapy in the third-line treatment of mCRC has been verified in some prospective and retrospective studies. In accordance with previous results, the ORR and DCR of this combination strategy achieved 16.7% and 83.3% in our study, respectively, which was higher than anti-angiogenic monotherapy (ORR: 2.6%, DCR: 47.4%).

Overall, 8.8% of patients receiving chemotherapy ± targeted drugs achieved PR, and 61.3% of them achieved disease control, demonstrating the efficacy of chemotherapy in third-line

Table 2. Third-line treatment patterns.

Characteristics	Number	%
Initiation time of third-line treatment		
Before 1 January 2019	138	63.3
After 1 January 2019	80	36.7
Third-line treatment		
Chemotherapy	57	26.1
Chemotherapy plus targeted drugs	86	39.4
Anti-angiogenic drugs	40	18.4
Anti-EGFR drugs	15	6.9
Immunotherapy plus anti-angiogenic drugs	14	6.4
Others	6	2.8
Third-line chemotherapy		
Chemotherapy rechallenge	93	65.0
New chemotherapy regimens	50	35.0
Third-line targeted drugs		
Targeted drugs rechallenge	76	47.8
New targeted drugs	83	52.2
Third-line anti-angiogenic therapy		
Yes	116	53.2
No	102	46.8
Third-line clinical trial		
Yes	41	18.8
No	177	81.2
Cycles of third-line treatment		
Median (range)	4 (1–43)	
Later-line treatment		
Yes	76	34.9
No	142	65.1

EGFR, epidermal growth factor receptor.

setting. Furthermore, it was shown that whether choosing new chemotherapeutic drugs or previous used regimens did not affect tumor remission (Table 4). Similarly, there was no association between tumor response assessment and targeted drugs rechallenge including anti-angiogenic and anti-EGFR agents (Table 4), indicating that anti-angiogenic therapy has sustainable benefits across lines, and the anti-EGFR rechallenge strategy is feasible in the third-line treatment of mCRC.

Survival outcomes of third-line treatment

In our cohort, the median follow-up time was 10.0 months (range: 1.0–48.0 months) of all patients receiving third-line therapy. Disease progression and time of death were recorded in 198 (90.4%, 198/218) and 172 patients (78.9%, 172/218), respectively. The median PFS3 and OS3 were 4.0 m (range: 0.5–26.0 m) and 10.7 m (range: 1.0–48.0 m) in all patients, respectively. Landmark PFS3 estimates at 6-, 12-, and 18-month after the start of third-line therapy were 35.2%, 8.6%, and 3.4%, respectively. And the 6-, 12-, 18-, and 24-month OS3 rates were 70.0%, 44.6%, 27.0%, and 13.5% for all patients, respectively.

Factors potentially associated with survival were analyzed using the Cox univariate analysis (Table 5). As the results shown, other than the front-line treatment benefits (defined as PFS1 + PFS2 $\geqslant$ 12 m) and third-line therapeutic regime, the remaining factors were not significantly associated with differential hazard for PFS3 at each time point during follow-up. After the multivariate analysis (Table 6), the two characteristics were found to be independent prognostic factors for PFS3. Furthermore, the univariate analyses showed that the location of primary tumor, the resection pattern of primary tumor, the third-line therapeutic regime and whether or not there was later-line treatment were related to OS3. Similarly, the third-line therapeutic regime and the later-line treatment were regarded as independent prognostic factors for OS3 after the multivariate adjustment. Compared to the survival of patients receiving anti-angiogenic monotherapy, the prognosis of patients receiving chemotherapy $\pm$ targeted drugs was better (Tables 5 and 6).

Moreover, survival curves were constructed with the Kaplan–Meier method. The median PFS3 of patients receiving chemotherapy $\pm$ targeted drugs, anti-angiogenic agents, anti-EGFR drugs, or immunotherapies were 4.9, 2.7, 3.0, or 6.0 m, respectively. The median OS3 of patients receiving

Table 3. Response assessment of third-line treatment.

Assessment	Chemotherapy ± targeted drugs	Anti-angiogenic drugs	Anti-EGFR drugs	Immunotherapy + anti-angiogenic drugs	Others
	No	No	No	No	No
CR	0	0	0	0	0
PR	12	1	6	2	0
SD	72	17	2	8	2
PD	53	20	6	2	3
ORR	8.8%	2.6%	42.9 %	16.7%	0%
DCR	61.3%	47.4%	57.1 %	83.3%	40.0%

CR, complete response; DCR, disease control rate; EGFR, epidermal growth factor receptor; ORR, overall response rate; PD, disease progression; PR, partial response; SD, stable disease.

Table 4. The association between tumor response assessment and types of chemotherapy or targeted drugs in third-line setting.

Characteristics	Assessment			χ^2	*p*
	PR	SD	PD		
Third-line chemotherapy				0.006	0.997
Chemotherapy rechallenge	8	48	35		
New chemotherapy regimens	4	24	18		
Third-line targeted drugs				2.697	0.260
Targeted drugs rechallenge	5	38	30		
New targeted drugs	11	40	25		
Third-line anti-angiogenic therapy				4.803[a]	0.094[a]
Previous use of anti-angiogenic therapy	2	37	27		
No	6	23	13		
Third-line anti-EGFR therapy				1.095[a]	0.801[a]
Previous use of anti-EGFR therapy	1	1	2		
No	7	14	9		

[a]Fisher exact probability test.
CR, complete response; EGFR, epidermal growth factor receptor; PD, disease progression; PR, partial response; SD, stable disease.

chemotherapy ± targeted drugs, anti-angiogenic agents, anti-EGFR drugs, or immunotherapies were 12, 5.2, 14.5, or 13 m, respectively. In agreement with the results of Cox analysis, the third-line treatment scheme [$p = 0.004$; Figure 2(a)] and the front-line treatment benefits [$p = 0.023$; Figure 2(b)] demonstrated an intense relationship with PFS3. Likewise, the third-line

Table 5. The Cox univariate analysis of mCRC patients receiving third-line treatment.

Factor	PFS3			OS3		
	p	HR	95% CI	*p*	HR	95% CI
Gender (Male *versus* Female)	0.335	0.868	0.650–1.158	0.619	0.925	0.678–1.260
Age (<60 *versus* ⩾60)	0.712	0.948	0.715–1.257	0.827	0.967	0.715–1.308
Location of primary tumor						
Transverse colon *versus* ascending colon	0.933	0.974	0.522–1.816	0.261	0.673	0.338–1.342
Descending colon *versus* ascending colon	0.933	1.029	0.529–2.001	0.677	1.158	0.581–2.309
Sigmoid colon *versus* ascending colon	0.979	1.005	0.691–1.462	0.748	0.939	0.640–1.377
Rectum *versus* ascending colon	0.745	0.933	0.613–1.419	**0.017**	**0.588**	**0.380–0.910**
Pathologic differentiation						
Well *versus* poorly	0.524	0.784	0.370–1.658	0.549	0.785	0.356–1.733
Moderately *versus* poorly	0.844	1.041	0.698–1.551	0.379	0.824	0.536–1.268
Resection of primary tumor (radical *versus* palliative resection)	0.721	0.945	0.691–1.291	**0.014**	**1.521**	**1.088–2.127**
Number of metastatic organs at third-line treatment	0.502	1.061	0.893–1.260	0.268	1.116	0.919–1.355
Front-line treatment benefits (PFS1 + PFS2 ⩾12 m *versus* <12 m)	**0.030**	**0.721**	**0.537–0.968**	0.358	0.864	0.632–1.181
Third-line treatment						
Anti-angiogenic drugs *versus* chemotherapy ± targeted drugs	**0.001**	**1.855**	**1.280–2.689**	**0.000**	**2.238**	**1.539–3.255**
Anti-EGFR drugs *versus* chemotherapy ± targeted drugs	0.769	1.086	0.625–1.888	0.759	0.910	0.500–1.658
Immunotherapy + anti-angiogenic drugs *versus* chemotherapy ± targeted drugs	0.525	0.811	0.426–1.546	0.555	0.762	0.308–1.882
Third-line chemotherapy (rechallenge *versus* New regimens)	0.790	1.051	0.730–1.512	0.355	1.208	0.809–1.803
Third-line targeted drugs (rechallenge *versus* new drugs)	0.883	0.975	0.698–1.362	0.299	0.824	0.572–1.187
Third-line anti-angiogenic therapy (previous use *versus* none)	0.725	0.930	0.619–1.396	0.443	0.843	0.544–1.305
Third-line anti-EGFR therapy (previous use *versus* none)	0.318	0.575	0.194–1.703	0.557	1.833	0.243–13.834
Later-line treatment (yes *versus* no)	–	–	–	**0.000**	**0.462**	**0.333–0.641**

CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival.
Bold represents statistical differences.

Table 6. The Cox multivariate analysis of mCRC patients receiving third-line treatment.

Factor	PFS3			OS3		
	p	HR	95% CI	*p*	HR	95% CI
Location of primary tumor						
Transverse colon *versus* ascending colon	–	–	–	0.114	0.505	0.217–1.178
Descending colon *versus* ascending colon	–	–	–	0.572	1.241	0.587–2.623
Sigmoid colon *versus* ascending colon	–	–	–	0.579	0.882	0.567–1.373
Rectum *versus* ascending colon	–	–	–	0.211	0.715	0.422–1.209
Resection of primary tumor (radical *versus* palliative resection)	–	–	–	0.426	1.168	0.797–1.712
Front-line treatment benefits (PFS1 + PFS2 ⩾12 m *versus* <12 m)	**0.046**	**0.732**	**0.538–0.995**	–	–	–
Third-line treatment						
Anti-angiogenic drugs *versus* chemotherapy ± targeted drugs	**0.023**	**1.619**	**1.068–2.455**	**0.000**	**2.730**	**1.751–4.258**
Anti-EGFR drugs *versus* chemotherapy ± targeted drugs	0.863	1.050	0.603–1.827	0.619	1.190	0.599–2.363
Immunotherapy + anti-angiogenic drugs *versus* chemotherapy ± targeted drugs	0.263	0.678	0.343–1.340	0.993	0.996	0.393–2.523
Later-line treatment (yes *versus* no)	–	–	–	**0.004**	**0.558**	**0.377–0.826**

CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival.
Bold represents statistical differences.

therapy [$p < 0.0001$; Figure 2(c)], later-line treatment [$p < 0.0001$; Figure 2(d)], and primary tumor resection types [$p = 0.012$; Figure 2(e)] were associated with OS3 in all patients. From the above results, it could be found that compared to other schemes, survival was the worst in patients who received anti-angiogenic monotherapy in the third-line setting. For patients who could benefit from front-line treatment, the PFS3 of third-line therapy was also relatively longer. If the patient was still in appropriate physical condition after the failure of third-line therapy and had opportunity to receive more later-line treatment, his OS would be prolonged.

A variety of drugs, including chemotherapeutic medicine (oxaliplatin, irinotecan, fluoropyrimidine, etc.), anti-angiogenic agents (bevacizumab, regorafenib, fruquintinib, etc.), and anti-EGFR drugs (cetuximab, panitumumab) have been approved for the treatment of mCRC. Immunotherapy is increasingly used to treat tumors; the efficacy of immune checkpoint inhibitors has been confirmed in mCRC. We further analyzed the effects of the types and amounts of drugs received by mCRC patients on OS. The results showed that in the whole-course management of mCRC patients, the more kinds and quantities of drugs patients received, the longer survival of them achieved (Figure 3), indicating that only by drawing up a reasonable arrangement of different drugs, can patients acquire the maximum survival benefit.

Discussion

To our knowledge, this is the first real-world study on the third-line treatment patterns and clinical outcomes for mCRC patients in China. In this study, we described patient demographics,

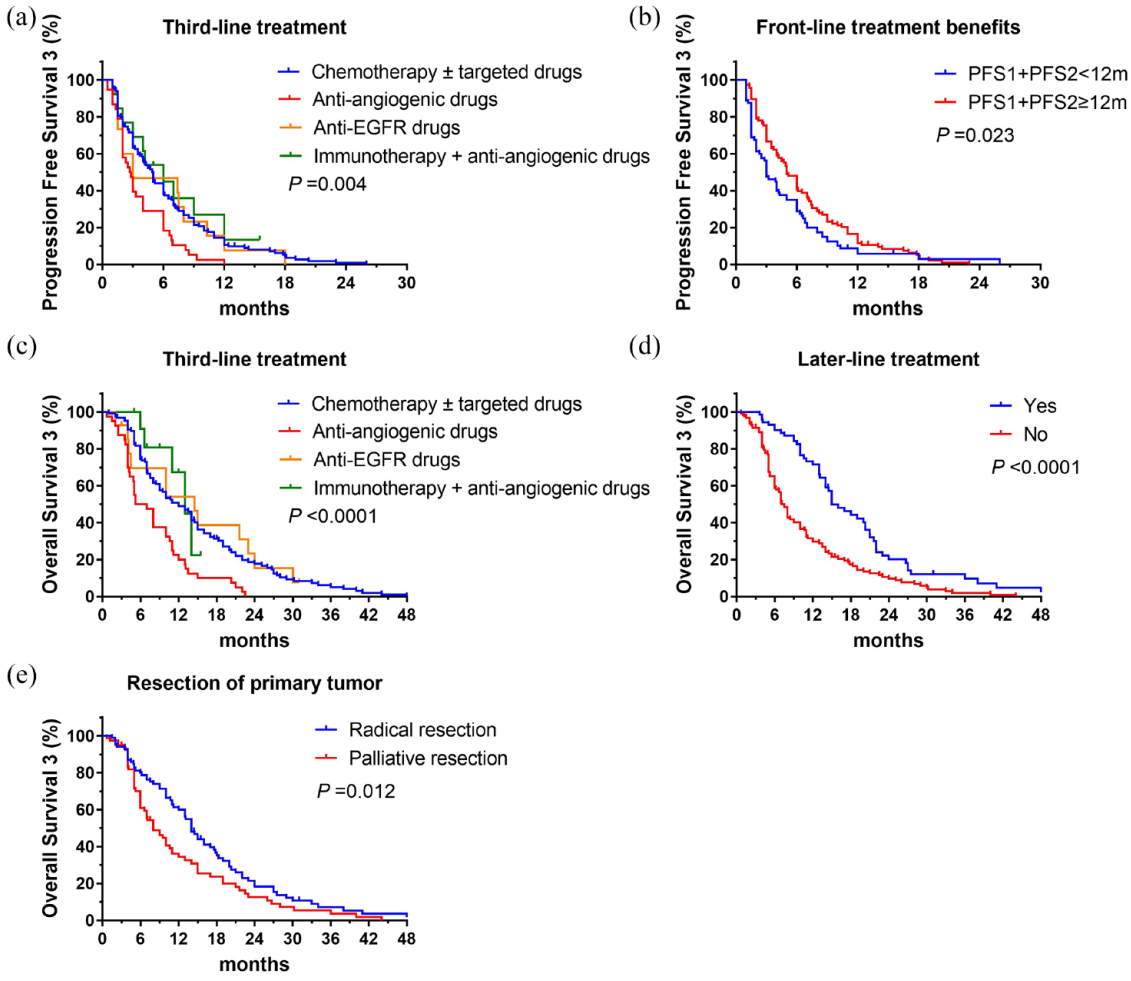

Figure 2. The survival curves of all patients in different groups. (a) and (b) The PFS curves of patients stratified by third-line treatment (a) and front-line treatment benefits (b). (c)–(e) The overall survival curves of patients stratified by third-line treatment (c), later-line treatment (d) and the resection of primary tumor (e). PFS, progression-free survival.

clinical characteristics, treatment schemes, and survival outcomes in detail, which provided a comprehensive and updated picture of Chinese mCRC patients.

The median age of mCRC patients in third-line setting during 2013 to 2020 was 58 years old, and there were more male CRC patients than females, which was in accordance with previous studies[26] and further confirmed the preventive effect of estrogen on CRC.[27] In our study, 31.7% of patients presented with Tumor Node Metastasis (TNM) stage III and 56.9% identified with stage IV at initial diagnosis. The percentage of mCRC patients is larger than that reported in other countries,[28] which may result from the differences in study samples and relative lower prevalence of early screening for CRC than western countries. More than 20% of patients had their primary tumors in the ascending colon, whereas left-sided CRC was diagnosed in nearly 70% of patients. Ageing is one of the reasons of the increased incidence rate of right-sided CRC, and the rightward shift in the primary tumor site of CRC was also verified in previous studies.[29]

As expected, the most commonly used first-line and second-line treatment regimens in our study were oxaliplatin-based therapies (69.3%) and irinotecan-based therapies (72.5%), which was in line with other real-world investigations.[25] From 2013 to 2019, we found that more and more patients had access to third-line therapy in our data, but the median treatment cycle in third-line

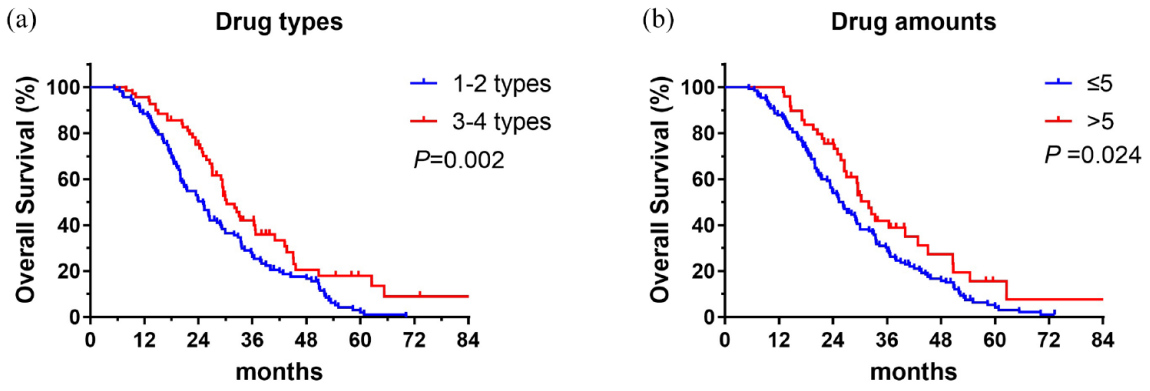

Figure 3. The OS curves based on drugs used in the whole-course of mCRC. (a) OS curves according to drugs types (chemotherapy, anti-angiogenic therapy, anti-EGFR therapy, immunotherapy). (b) OS curves according to drugs amounts.
EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; OS, overall survival.

was less than that in front-line. Despite the lack of consensus on third-line treatment, the majority of patients moved back to their previously used therapies including chemotherapeutic drugs (rechallenge rate: 65%) and targeted agents (rechallenge rate: 47.8%). Our study also found that chemotherapy combined with or without targeted drugs remained the mainstream choice of third-line treatment at that time, which was controversial to the guidelines for CRC. This gap between clinical practice and guidelines may be due to drug accessibility, patients' preference, economic status, and physicians' decisions.

A large number of studies have evaluated the efficiency of different treatment options for third-line treatment of mCRC. In addition to the standard third-line recommended drugs regorafenib[16,30] and fruquintinib,[31] the efficacy of other anti-angiogenic agents, such as apatinib[32] and anlotinib,[33] was verified. However, the ORR and survival outcomes of the third-line anti-angiogenic therapy in our study are slightly inferior to previous data, which may result from the limited samples in this group. Besides, a retrospective study discovered that patients treated with TAS-102 had better tumor response and disease control than patients treated with regorafenib,[34] indicating the superiority of chemotherapeutic drugs in third-line setting. The clinical benefit rate of oxaliplatin or irinotecan-based rechallenge was reported to be 75.5%.[35] From the Retreatment with Oxaliplatin-Based Regimenin Metastatic Colorectal Cancers (RETROX-CRC) retrospective study collecting 119 mCRC patients, the ORR and DCR of oxaliplatin retreatment were recorded as 21.6% and 57.8%, respectively.[36] Our study also found that the DCR of chemotherapy ± targeted drugs in the third-line setting could reached 61.3%, and the survival of those patients was longer than that of patients receiving anti-angiogenic monotherapy, which was consistent with another Japanese study.[24] Conversely, a retrospective multicenter clinical analysis containing 105 patients with mCRC concluded that anlotinib ($n = 35$) had better clinical efficiency as a third-line treatment than chemotherapy ($n = 35$) and similar to fruquintinib or regorafenib ($n = 35$).[33] The chemotherapy regimen included irinotecan combined with raltitrexed or raltitrexed only in their study.[33] The inferiority of chemotherapy might be related to drug selection to some extent. Those inconsistent results from small sample indicate that there is an urgent need for studies with larger sample size for stratified analysis in third-line decision-making.

However, biomarkers to guide the choice of third-line or later-line management remain unclear. The efficacy of regorafenib might be associated with specific genetic aberrations, such as APC mutation and FGFR1 amplification.[37] Additional analyses of RAS/RAF status could contribute to the selection of mCRC patients who are likely to benefit from third-line anti-EGFR drugs, regardless of primary tumor location.[38] Except for genetic status, pretreatment neutrophil-to-lymphocyte ratio, and carcinoembryonic antigen (CEA) levels could serve as potential biomarkers for patient selection, and treatment-induced neutropenia predicted response of TAS-102.[39] The latest discovery

suggests that codon-specific KRAS mutations can predict survival benefit of TAS-102.[40] In our study, we found that the benefits from front-line therapy was an independent indicator for PFS of third-line therapy. The similar results were reported in another chemotherapy rechallenge study from Turkey.[41] Undoubtedly, these above conclusions need to be further verified in larger studies.

Since there are multiple options for later-line therapy of mCRC patients at present, rational treatment sequencing is critical to further prolong their survival. Previous study concluded that the therapeutic sequence of regorafenib followed by cetuximab suggested a longer OS than the opposite sequence,[42] demonstrating the importance of optimized arrangement. Although we did not make an in-depth analysis of the sequence of the later-line treatment, we found that patients treated with more effective drugs could achieved better prognosis, and receiving fourth-line or above treatment was an independent protective factor for OS, which also confirmed the essential role of management of later-line treatment of mCRC.

This study had several limitations. First, the status of molecular markers, especially the RAS/RAF status, is important and essential information for guiding treatment decisions in patients with mCRC. RAS/RAF mutations are associated with patient prognosis and treatment choices, and various guidelines consider RAS/RAF status as the most important stratification factor. However, in this retrospective study, we only collected detailed genetic testing results from 125 patients (including 67 RAS/RAF wild-type and 58 RAS/RAF mutant-type) from electronic medical records and ultimately failed to conduct statistical analysis of RAS/RAF status. In the future, we will try to track the genetic test results of these patients again for biomarker analysis. The survival of the anti-angiogenic monotherapy group in this study was slightly worse than the results of clinical trials, which may be related to the RAS/RAF status of patients in this group. In addition to the genetic detection results, adverse effects were not recorded in detail in the electronic medical records due to outpatient treatment; thus, we did not describe and analyze these characteristics. Second, our sample population was from a single tertiary hospital and was relatively small compared to the worldwide collaborative CRC database, and thus discrepancies with other datasets cannot be excluded. Lastly, our research was retrospective in nature. We collected consecutive mCRC patients who received third-line therapy between January 2013 and December 2020; thus, the calculation of the sample size selected in this study was not performed. The convincing power was limited. However, the high uniformity of therapy procedures and patient follow-up throughout the entire study period can help guarantee our conclusions. Larger prospective trails or real-world analyses are needed to further consolidate our findings.

Conclusion

To conclude, chemotherapy combined with or without targeted therapy remained dominated in the third-line treatment and showed more favorable efficacy than anti-angiogenic monotherapy in this real-world study of mCRC, suggesting that in the era of rapid progress in the targeted therapy and immunotherapy, the use of traditional chemotherapy in the third-line setting can still bring favorable survival benefits to patients with mCRC. It is also indicated that in the third-line decision-making, just like choosing regorafenib or TAS-102, clinicians can also consider traditional chemotherapy, especially in suitable patients, which may leave more drug choices in their later-line therapy. Our research indeed confirmed that the more drugs used throughout the entire course of mCRC, the more likely they are to achieve long-term survival. However, because of the limited sample size and incomplete biomarker data, our study is difficult to further analyze and find biomarker to guide stratified treatment, in other words, which group of patients are more suitable for particular chemotherapy or anti-angiogenic monotherapy or others. Future research with a large sample size and detailed biomarker data will ultimately achieve a roadmap for the third-line stratified treatment.

Declarations

Ethics approval and consent to participate

The study protocol (Supplemental Figure 1) was reviewed and approved by Tianjin Medical University Cancer Institute and Hospital Review Board. Because this was a retrospective study that only collected real-world treatment information from patients without affecting any clinical outcomes, the ethical approval and the requirement

for informed consent from each patient was waived in accordance with institutional regulations.

Consent for publication
Not applicable.

Author contributions
Ting Deng: Conceptualization; Data curation; Investigation; Writing – review & editing.

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Rui Liu: Data curation; Formal analysis; Writing – review & editing.

Tao Ning: Investigation; Methodology; Writing – original draft.

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Competing interests
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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Supplemental material
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