



Effects of multidisciplinary team on the outcomes of colorectal cancer patients with liver metastases

Xingchen Li[#], Qichen Chen[#], Xinyu Bi, Jianjun Zhao, Zhiyu Li, Jianguo Zhou, Zhen Huang, Yefan Zhang, Rui Mao, Hong Zhao, Jianqiang Cai

Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Contributions: (I) Conception and design: J Cai, H Zhao; (II) Administrative support: H Zhao, J Cai; (III) Provision of study materials or patients: Y Zhang, Z Huang; (IV) Collection and assembly of data: X Li, Q Chen; (V) Data analysis and interpretation: X Li, Q Chen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Jianqiang Cai; Hong Zhao. Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17 Nanli, Panjiayuan, Chaoyang District, Beijing 100021, China. Email: caijianqiang@picam.ac.cn; zhaohong@picam.ac.cn.

Background: To evaluate the effect of a multidisciplinary team (MDT) treatment modality on outcomes of patients with colorectal cancer with liver metastases (CRLMs) in China.

Methods: We retrospectively identified 236 (MDT: 46, non-MDT: 190) patients who underwent liver resection or simultaneous resection for primary colorectal cancer and liver metastases with a curative intent for CRLMs at the National Cancer Center between January 2014 and June 2018. A 1:2 propensity score matching (PSM) analysis was used to adjust for differences in baseline characteristics between the MDT group and the non-MDT group. After the 1:2 PSM analysis, 46 patients were assigned to the MDT group, and 83 patients were assigned to the non-MDT group. All statistical analyses were performed using SPSS Statistics, version 22 (Armonk, NY, USA). Statistical significance was set at a 2-sided $P < 0.05$.

Results: Before PSM analysis, compared to non-MDT patients, MDT patients had worse biological characteristics and were more likely to have node-positive primary tumors (80.4% *vs.* 63.2%), multiple liver metastases (73.9% *vs.* 50.5%), and liver metastases with a bilobar distribution (73.9% *vs.* 50.5%). However, MDT patients had a tendency towards better overall survival (OS) ($P = 0.169$, median OS: 49.7 *vs.* 35.2 months). After PSM analysis, no differences in clinicopathologic parameters were identified between the MDT group and the non-MDT group. Compared to non-MDT patients, MDT patients had a tendency towards better OS ($P = 0.063$, median OS: 49.7 *vs.* 34.1 months). Multivariate analysis showed that having an MDT (HR, 0.550, 95% CI: 0.309–0.977, $P = 0.041$) was an independent predictor of better OS.

Conclusions: The MDT treatment modality can significantly improve the outcomes of CRLMs patients with poor biological characteristics in China.

Keywords: Multidisciplinary team (MDT); colorectal cancer with liver metastases (CRLMs); propensity score matched; outcomes

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Introduction

The incidence of colorectal cancer increases each year, ranking third of all malignant tumors. Colorectal cancer is the second leading cause of cancer death (1). The liver is the most common target organ for colorectal cancer metastasis, which is a significant cause of death (2). Approximately 15–25% of patients with colorectal cancer have liver metastasis at the initial diagnosis, and nearly 25% of colorectal cancer patients still have heterogeneous liver metastasis after primary tumor resection (3). The median overall survival (OS) time of patients without treatment after liver metastasis is only 6.9 months (4). Although chemotherapy can prolong the survival time of patients with liver metastasis from colorectal cancer, if the liver metastases cannot be removed, the 5-year survival rate of patients is close to zero (5). However, if R0 resection of primary tumors and liver metastases can be achieved, the 5-year survival rate can be as high as 30–57% (6–9). Five-year OS of patients with simultaneous resection of primary tumors and liver metastases in our center is 47.8%. One study showed that some patients with initial liver metastases that could not be eradicated could undergo resection or achieve no evidence of disease (NED) after neoadjuvant chemotherapy (NAC) (4). Improving the R0 resection rate and converting unresectable liver metastasis into resectable liver metastasis are key for improving the therapeutic effect for patients with colorectal cancer with liver metastases (CRLMs) and are the focus of clinical research at present.

Therefore, the multidisciplinary team (MDT) for patients with CRLMs should conduct a comprehensive personalized assessment to make treatment decisions, develop an appropriate plan, prevent the occurrence of CRLMs and improve the R0 resection rate and 5-year survival rate (10,11). MDT has become increasingly popular forms of diagnosis and treatment in clinical work in recent years. The core of the MDT is a patient-centered focus, and multiple experts, including those from surgery, oncology, radiology, pathology and other related disciplines, hold discussions to define the most accurate diagnostic stage for patients and to develop the most appropriate treatment plan. Several studies have shown that patients with CRLMs have an improved prognosis with an MDT diagnosis and treatment model, and many studies have shown that having an MDT is an independent predictor of a good prognosis in colorectal cancer patients (12,13). Therefore, international guidelines (including 2019NCCN, 2019CSCO and 2016ESMO) and expert consensus all recommend the

diagnosis and treatment of CRLMs with the MDT treatment model. An MDT can not only clarify the diagnosis and treatment plan of patients and improve their prognosis but also promote communication and discussion among different disciplines, enhance the academic atmosphere of the hospital, promote the development and enrollment of clinical trials, and improve the professional level of young doctors.

In recent years, MDT have been established in an increasing number of medical centers, there are a large number of CRLM patients in China, and the implementation of standardized MDT modality is conducive to the diagnosis and treatment of CRLM patients, but the implementation of MDT in some non-specialized hospitals is still not standardized, furthermore, few studies have been conducted in patients with CRLMs treated with surgery. There is still a lack of high-quality research to explore the advantages of MDT modality in CRLM patients in China. In addition, medical centers are more inclined to include advanced or intractable cases in MDT, which leads to differences in baseline clinicopathological features between the MDT group and the non-MDT group, and the baseline data of these included patients have not been strictly matched and analyzed, with inconsistent intervention measures and differences in tumor stage, metastatic tumor number, CRS score, etc.; thus, the conclusions are controversial. In this study, we compared the prognosis of patients with CRLMs during the same period with or without MDT involvement through propensity score matching (PSM) analysis. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/apm-20-193>).

Methods

Patients and treatment

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study (ID: NCC2019C-016) was approved by the Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences ethics board of, NCC2019C-016 and informed consent was taken from all the patients.

After receiving ethical approval from the Institutional Review Board, we conducted a retrospective analysis of 236 consecutive cases of pathologically diagnosed CRLM patients receiving their first liver resection at our hospital between January 2014 and June 2018. Patients with (n=46)

and without (n=190) MDT involvement were selected. Patients in the two groups were matched at a ratio of 1:2 through PSM, and a total of 129 patients were included in the study: 46 patients with an MDT and 83 patients without an MDT. After PSM, no significant differences in baseline parameters were identified between the patients in the two groups ($P>0.05$). Synchronous CRLM was defined as the detection of liver metastasis during the diagnosis of the primary tumor or within the first 6 months. CRLM patients with high clinical risk-scoring system scores or initially unresectable liver metastases were recommended to receive NAC (14,15). The NAC regimens consisted of 5-fluorouracil/capecitabine and oxaliplatin or irinotecan. Liver resection was defined as major or minor resection. Resection of one segment was defined as minor liver resection. Surgical resection included open and laparoscopic approaches. The severity of postoperative complications was described according to the Clavien-Dindo classification system, and major complications were classified as Clavien-Dindo III–V (16). Patients received adjuvant chemotherapy according to the histological stage and the resection margin status. After recurrence, patients received chemotherapy, TACE or surgery.

The MDT consisted of faculty from medical oncology and surgical oncology as well as radiologists and pathologists. The treatment guidelines for CRLM in our hospital were established after group discussion and modification of the guidelines according to the latest version of the MDT guidelines. The treatment protocols for patients with CRLM after MDT discussion and any deviation from the protocol were recorded. For patients with an MDT, the chemotherapy regimen, chemotherapy cycle, timing of the operation, operative approach and treatment strategies after recurrence were all determined by the MDT.

Outcome and statistical analysis

The endpoint of interest was OS, which was defined as the interval from the date of liver resection to the date of death or the last follow-up. Categorical clinical variables were compared using the chi-square test or Fisher's exact test, and numerical variables were examined by the Mann-Whitney U test. Survival was compared by a log-rank test and calculated with the Kaplan-Meier method. Independent variables with $P<0.10$ on univariate analysis were included in multivariate models. Forward logistic regression in the multivariate analysis was used to investigate independent factors of survival. A 1:2 PSM analysis was used to adjust

for differences in baseline characteristics between the MDT group and the non-MDT group. All statistical analyses were performed using SPSS Statistics, version 22 (Armonk, NY, USA). Statistical significance was set at a 2-sided $P<0.05$.

Results

Clinicopathologic Characteristics

Among the 236 patients, most were male, and the median age was 58 years (IQR 51–64). The proportion of primary tumors located in the rectum was 42.8%. One hundred eighty-two patients (77.1%) had synchronous CRLM. The median diameter of the largest lesion was 2.5 (IQR 1.7–4.0) cm, and 44.1% of the patients had a lesion larger than 3 cm. Of these patients, 55.1% had more than one liver metastasis, with a median of 2 lesions (IQR 1.0–4.0). The T3–T4 stage was observed in 91.9% of the patients. A node-positive primary tumor was observed in 66.5% of the patients. Ninety-four patients (39.8%) received NAC. Adjuvant chemotherapy was received by 142 (60.2%) patients. Liver metastases with a bilobar distribution were observed in 93 (39.4%) patients. Seventy-seven patients (32.6%) received major liver resection, and 165 patients (69.9%) underwent synchronous CRLM resection. Forty-six patients had an MDT throughout the whole therapy process. The median number of MDTs was 2 (IQR 1–3). Among the patients, 43.6% (103/236) had postoperative complications.

No differences in the age at surgery, gender, comorbidities, preoperative carcinoembryonic antigen (CEA), metastasis diameter, tumor differentiation and primary tumor T stage were identified between the MDT group and the non-MDT group. Conversely, compared to non-MDT patients, MDT patients have worse biological characteristics and were more likely to be treated with NAC (58.7% *vs.* 35.3%) and to have node-positive primary tumors (80.4% *vs.* 63.2%), multiple liver metastases (73.9% *vs.* 50.5%), and liver metastases with a bilobar distribution (73.9% *vs.* 50.5%). After 1:2 PSM, 46 patients were assigned to the MDT group, and 83 patients were assigned to the non-MDT group. No differences in clinicopathologic parameters were detected between the MDT group and the non-MDT group. The detailed clinicopathologic parameters of the two groups of patients are compared in *Table 1*.

Impact of the MDT on survival before PSM

The median follow-up was 32 months. At the

Table 1 Patient and tumor characteristics

Item	Before 1:2 propensity matching				After 1:2 propensity matching			
	Non-MDT (n=190)	MDT (n=46)	P	All patients (n=236)	Non-MDT (n=83)	MDT (n=46)	P	All patients (n=129)
Age >60 years, n (%)	90 (47.4)	16 (34.8)	0.124	106 (44.9)	42 (50.6)	16 (34.8)	0.084	58 (45.0)
Male, n (%)	112 (58.9)	32 (69.6)	0.185	144 (48.3)	54 (65.1)	32 (69.6)	0.603	86 (66.7)
Preoperative CEA >10 ng/mL, n (%)	87 (45.8)	22 (47.8)	0.804	109 (46.2)	39 (47.0)	22 (47.8)	0.927	61 (47.3)
Synchronous metastasis, n (%)	142 (74.7)	40 (87.0)	0.077	182 (77.1)	70 (84.3)	40 (87.0)	0.688	110 (85.3)
Right hemicolon, n (%)	37 (19.5)	8 (17.4)	0.747	45 (17.1)	14 (16.9)	8 (17.4)	0.940	22 (17.1)
R0 resection, n (%)	123 (64.7)	25 (54.3)	0.191	148 (62.7)	45 (54.2)	25 (54.3)	0.989	70 (54.3)
Major liver resection, n (%)	64 (33.7)	13 (28.3)	0.481	77 (32.6)	31 (37.3)	13 (28.3)	0.297	44 (34.1)
Heterochronous resection, n (%)	59 (31.1)	12 (26.1)	0.510	71 (30.1)	14 (16.9)	12 (26.1)	0.211	26 (20.2)
Bilobar distribution, n (%)	65 (34.3)	28 (60.9)	0.001	93 (39.4)	49 (59.0)	28 (60.9)	0.839	77 (59.7)
Extrahepatic metastases, n (%)	23 (12.1)	7 (15.2)	0.570	30 (12.7)	12 (14.5)	7 (15.2)	0.907	19 (14.7)
Diameter of metastases >3 cm, n (%)	85 (44.7)	19 (41.3)	0.674	104 (44.1)	42 (50.6)	19 (41.3)	0.311	61 (47.3)
Multiple metastases, n (%)	96 (50.5)	34 (73.9)	0.004	130 (55.1)	61 (73.5)	34 (73.9)	0.959	94 (72.9)
Poor differentiation, n (%)	52 (27.4)	15 (32.6)	0.479	67 (28.4)	25 (30.1)	15 (32.6)	0.770	40 (31.0)
pT3–T4, n (%)	176 (92.6)	41 (89.1)	0.434	217 (91.9)	77 (92.8)	41 (89.1)	0.478	118 (91.5)
Node-positive primary tumor, n (%)	120 (63.2)	37 (80.4)	0.026	157 (66.5)	65 (78.3)	37 (80.4)	0.777	102 (79.1)
Complications, n (%)	81 (42.6)	22 (47.8)	0.524	103 (43.6)	39 (47.0)	22 (47.8)	0.927	61 (47.3)
Neoadjuvant chemotherapy, n (%)	67 (35.3)	27 (58.7)	0.004	94 (39.8)	43 (51.8)	27 (58.7)	0.452	70 (54.3)
Postoperative chemotherapy, n (%)	109 (57.4)	33 (71.7)	0.074	142 (60.2)	51 (61.4)	33 (71.7)	0.240	84 (65.1)

time of analysis, 86 patients (36.4%) had died, and 181 patients (76.7%) had experienced disease recurrence. The median OS was 41.9 (95% CI: 32.6–51.2) months, and the median progression-free survival (PFS) was 10.0 (95% CI: 8.4–11.6) months. The 1- and 3-year survival rates were 94.4% and 53.5%, respectively. The 1- and 3-year PFS rates were 40.1% and 19.8%, respectively. Compared to non-MDT patients, MDT patients had a tendency towards better OS ($P=0.169$, median OS: 49.7 vs. 35.2 months) (Figure 1). Univariate analysis revealed that non-R0 resection, complications, multiple liver metastases and neoadjuvant chemotherapy were associated with decreased OS. Multivariate analysis revealed that R0 resection, complications and adjuvant chemotherapy were independent predictors of OS (Table 2). However, multivariate analysis revealed that having an MDT was not an independent predictor of OS.

Impact of the MDT on survival after PSM

A 1:2 PSM analysis was used to adjust for differences in baseline characteristics between the MDT group and the non-MDT group. The median OS and the median PFS were 41 (95% CI: 33.1–48.9) months and 7.2 (95% CI: 5.0–9.4) months, respectively. The 1- and 3-year survival rates were 94.6% and 52.2%. The 1- and 3-year PFS rates were 34.9% and 16.9%, respectively. Compared to non-MDT patients, MDT patients had a tendency towards better OS ($P=0.063$, median OS: 49.7 vs. 34.1 months) (Figure 2). Multivariate analysis showed that having an MDT (HR, 0.550, 95% CI: 0.309–0.977, $P=0.041$) was an independent predictor of better OS (Table 2).

Discussion

This study is the first to confirm that having an MDT

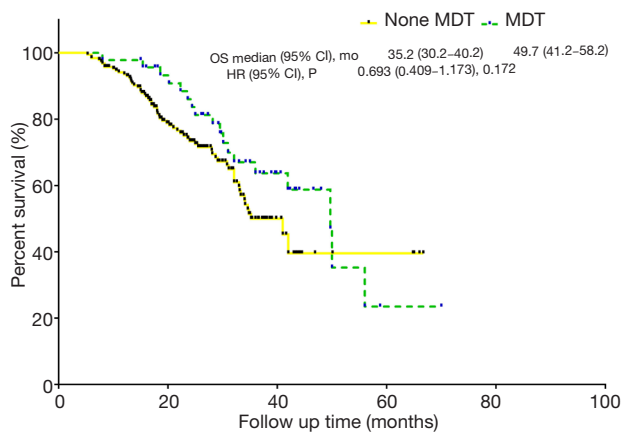


Figure 1 OS analysis of non-MDT versus MDT patients before propensity matching. OS, overall survival; MDT, multidisciplinary team.

as an independent prognostic factor for patients with CRLMs undergoing surgical treatment after PSM. In addition, multivariate analysis showed that R0 resection and postoperative chemotherapy were also independent factors affecting the prognosis. Compared to non-MDT patients, MDT patients were more likely to be treated with NAC (58.7% *vs.* 35.3%) and to have lymph node-positive primary tumors (80.4% *vs.* 63.2%), multiple liver metastases (73.9% *vs.* 50.5%), and liver metastases with a bilobar distribution (73.9% *vs.* 50.5%). Patients matched for MDTs had a relatively advanced disease period, but no difference in OS was found ($P=0.172$). After PSM, having an MDT was an independent prognostic factor for postoperative OS [$P=0.041$; HR (95% CI): 0.550 (0.309–0.977)]. We demonstrated the importance of MDT in the prognosis of patients with CRLMs from different perspectives. The contribution of a MDT includes increased application of NAC, advanced stage of patients received more standard comprehensive treatment, a larger proportion of patients received NAC through MDT, most of which were advanced stage and benefited significantly from NAC. In addition, careful selection of patients for appropriate treatment is important but complex. The patient's performance status, the stage of the primary tumor, the extent of the metastatic disease and the surgical or anesthesia risk of the patient should all be carefully considered. All of these factors rely on full discussion and coordination of different specialists who are involved in colorectal cancer treatment. As a result, patients can benefit from comprehensive treatment.

In recent years, the advancement of neoadjuvant therapy

has substantially increased the likelihood of R0 surgery for CRLM patients, increased the volume of the remaining liver after surgery, and improved the survival rate (17,18). Nearly 80% of CRLMs in patients are unresectable at initial diagnosis, and 12.5% of CRLMs are resectable through conversion therapy (19). However, the 5-year survival rate of these patients is similar to that of patients with resectable disease at the initial diagnosis (20). Therefore, under the premise of effective treatment, both conversion therapy and neoadjuvant therapy seem to improve the overall prognosis of CRLM patients. Additionally, in this study, patients with MDT involvement were more likely to be treated with NAC (58.7% *vs.* 35.3%), which may be one of the factors resulting in patients treated for CRLMs having a relatively good prognosis after MDT collaboration.

Before the 1990s, surgical treatment was the primary choice for colorectal cancer, and then a variety of comprehensive treatment methods and concepts were applied in the clinical treatment of colorectal cancer. After entering the 21st century, MDT was gradually established in major medical centers, and their advantages have steadily emerged. Since 1998, our hospital has had an established multidisciplinary comprehensive outpatient service. In 2008, an MDT for digestive tract tumors was formally established, and case discussions were regularly organized at least once a week to facilitate preliminary screening, examination and treatment follow-up by the MDT. MDT can also reduce the number of imperfect decisions made by individual physicians (21). In addition, the important functions of and outcomes with MDT include (I) highly accurate disease staging (22); (II) limited confusion and delays in treatment; (III) highly personalized evaluation systems and treatments; (IV) good treatment cohesion; (V) high quality of life (23); and (VI) optimal clinical and survival benefits (13,14).

MDT have demonstrated advantages not only in the field of digestive tract tumors but also in various fields of oncology (24). However, no strict matching analysis was conducted for the patient data included in previous studies; thus, the results may have some heterogeneity. Although PSM was used in this study to match patients' baseline data, there certain limitations remained. (I) Differences in neoadjuvant/adjuvant chemotherapy regimens were not included among the prognostic indicators, and differences in efficacy evaluations between these chemotherapy regimens and patients may lead to heterogeneity in the conclusions. (II) Not all CRLM patients were assigned to an MDT at the initial diagnosis. Some patients chose an MDT only when the initial diagnosis was difficult or when they

Table 2 Univariate and multivariate analyses of predictive factors of OS for CRLM patients

Factor	Before 1:2 propensity matching			After 1:2 propensity matching		
	Univariate analysis		Multivariate analysis	Univariate analysis		Multivariate analysis
	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)
Age >60 years	0.882	1.034 (0.664–1.611)			0.474	1.225 (0.702–2.138)
Male	0.682	1.096 (0.707–1.700)			0.443	1.258 (0.700–2.259)
Preoperative CEA >10 ng/mL	0.323	1.243 (0.807–1.916)			0.338	1.302 (0.758–2.237)
Synchronous metastasis	0.648	0.888 (0.532–1.481)			0.439	0.742 (0.348–1.580)
Right hemicolon	0.531	1.191 (0.689–2.060)			0.473	1.288 (0.645–2.574)
R0 resection	0.003	0.520 (0.338–0.799)	0.006	0.542 (0.352–0.836)	0.001	0.389 (0.224–0.674)
Major liver resection	0.996	0.999 (0.592–1.683)			0.917	1.036 (0.534–2.010)
Bilobar distribution	0.051	1.532 (0.999–2.352)			0.238	1.397 (0.801–2.436)
Extrahepatic metastases	0.081	1.646 (0.940–2.884)			0.092	1.776 (0.911–3.463)
Diameter of metastases ≥3 cm	0.081	1.465 (0.953–2.250)			0.145	1.494 (0.871–2.564)
Multiple metastases	0.039	1.613 (1.024–2.539)			0.400	1.318 (0.693–2.507)
Complications	0.007	1.816 (1.179–2.796)	0.039	1.588 (1.023–2.463)	0.017	1.936 (1.126–3.329)
MDT	0.172	0.693 (0.409–1.173)			0.066	0.584 (0.329–1.037)
Poor differentiation	0.705	0.911 (0.562–1.476)			0.877	0.956 (0.541–1.688)
pT3–T4	0.842	0.919 (0.399–2.113)			0.899	1.069 (0.384–2.971)
Node-positive primary tumor	0.264	1.326 (0.808–2.175)			0.993	1.003 (0.487–2.067)
Heterochronous resection	0.328	1.258 (0.795–1.990)			0.441	1.290 (0.675–2.463)
Neoadjuvant chemotherapy	0.759	0.934 (0.605–1.444)			0.332	0.764 (0.444–1.315)
Postoperative chemotherapy	0.002	0.509 (0.331–0.784)	0.006	0.543 (0.351–0.840)	0.000	0.318 (0.184–0.554)

OS, overall survival; CRLM, colorectal cancer with liver metastasis.

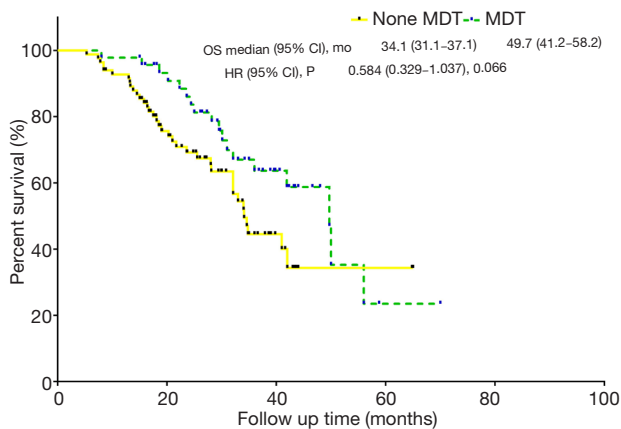


Figure 2 OS analysis of non-MDT versus MDT patients after propensity matching. OS, overall survival; MDT, multidisciplinary team.

changed their treatment plan, and a clear inclusion criterion was not determined. (III) This study was a retrospective study with low evidence for evidence-based medicine.

Conclusions

Overall, MDT demonstrated benefits for survival in patients with CRLMs. The importance of MDT in comprehensive treatment models should be scientifically recognized for CRLM patients.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/apm-20-193>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study (ID: NCC2019C-016) was approved by the Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences, and informed consent was taken from all the patients.

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