Local treatment combined with chemotherapy improves survival of patients with pulmonary metastases of colorectal cancer—a real-world retrospective study

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Abstract

Background The effect of local treatments for pulmonary metastases from colorectal cancer (CRC-PM) remains controversial. This study aims to figure out whether local treatments combined with chemotherapy could improve patients’ survival by comparing the outcomes of CRC-PM patients who submitted to local interventions combined with chemotherapy or just chemotherapy.

Patients and Methods From January 2009 to July 2019, a total of 119 patients with CRC-PM from two surgical centers were reviewed. Patients were divided into two groups according to treatments for the lung metastases: Local intervention combined with chemotherapy (Group-LI) and Chemotherapy alone (Group-Chem). Overall survival (OS) and progression-free survival (PFS) were assessed with the Kaplan-Meier method. Clinical characteristics associated with prognosis were analyzed by using a Cox proportional hazards regression model. Propensity score matching analyses were used to overcome the possible biases in some baseline characteristics.

Result Multivariable analysis revealed that the level of carinoembryonic antigen (CEA) and treatment for CRC-PM are independent predictors of both OS and PFS. The median OS in Group-LI (n = 39) and Group-Chem (n = 80) were 34.5 months and 13.8 months, respectively (P < 0.001). The 3-year progression-free survival rate in Group-LI and Group-Chem were 75.2% and 45.1% (P < 0.001). After propensity score matching, patients in Group-LI had better OS (HR = 3.304, P = 0.022) and PFS (HR = 4.029, P < 0.001) than Group-Chem.

Conclusion. CRC-PM patients with lower lever of CEA or local treatment of lung metastases are more likely to be those with favorable prognosis. Selected CRC-PM patients could benefit from local treatment of pulmonary metastases.

Introduction

Colorectal cancer (CRC) is one of the common malignancies all over the world, the incidence rate of CRC ranks the fourth among all malignant tumors (6.1%), while its mortality rate is the second highest (9.2%)[1]. In recent years, profit from colorectal cancer screening, early detection and improvement of treatment, the survival of patients with colorectal cancer has been significantly improved. However, the prognosis of patients with advanced colorectal cancer remains poor (median survival of 30 months). According to the statistics, 25% of newly diagnosed patients with colorectal cancer have distant metastases, and another 25% of patients with localized cancer newly diagnosed will develop distant metastases in the future[2]. Therefore, how to improve the survival of patients with advanced CRC is of intractability, and this has attracted more and more attention of clinicians in recent years.

The concept of oligometastasis was first proposed by Samuel Hellman and Ralph Weichselbaum in 1995[3]. It was described as “the existence of metastases at up to 2 or occasionally 3 sites and 5 or sometimes more lesions, predominantly visceral and occasionally lymphonodal” in ESMO consensus guidelines[4].The guidelines recommend that patients with oligometastatic disease should take active treatment as far as possible. The most common metastatic site of colorectal cancer is the liver, which accounts for 20%-70% of patients with advanced colorectal cancer. Many researchers have done a lot of work on how to deal with liver metastases. Radical resection, radiofrequency ablation, and interventional treatment for liver metastases have been a commonly accepted option due to their effectiveness in local control of the metastases and improvement of patients’ prognosis.

The lung is the second most common metastatic site in CRC, with 10–20% reported in the literature[5, 6]. Comparing with hepatic metastases, pulmonary metastasis from colorectal cancer seems to be less severe. The progress of CRC-PM is slow, and few patients have respiratory-related symptoms, which means it does not have a significant impact on the quality of life. Patients with CRC-PM have a better prognosis than other advanced patients. Therefore, treatment of lung metastases from colorectal cancer has not received as much attention as liver metastases. In recent years, with the development of medical technique, especially high-resolution
computed tomography (CT), the detection rate of CRC-PM has increased, and how to treat lung metastases has received more attention. Traditionally, systemic chemotherapy is the core of treatments for CRC-PM. There were a small group of selected CRC patients take local interventions for lesions in the lung. Pulmonary resection for metastases is currently a widely accepted method for CRC-PM. The NCCN guidelines recommend that CRC-PM patients who are submitted to lung surgery should meet some criteria, including the possibility to complete resection with maintenance of adequate function and R0 resection for primary site. The guidelines also indicate that resectable extrapulmonary metastases is not contraindications to surgery. In some cases, ablative techniques and radiation therapy could be considered as options[7]. These recommendations based on multiple retrospective analyses, but not high-quality evidence like RCT research. Some of these retrospective studies have pointed out that surgical removal of lung metastases can improve the 5-year overall survival rate (25–50%) of highly selected patients. Recent studies have also pointed out that local treatment of CRC-PM, such as radiofrequency ablation, targeted radiotherapy and other measures are also effective therapies that have good local control rates in patients with pulmonary metastases from colorectal cancer. However, as selection bias exists and indications for surgery remains unclear, there is still no strong evidence to support whether local interventions can improve the prognosis of patients.

Given that the indications for surgery for lung metastasis have not been clarified, it might be more feasible to compare the clinical outcomes of CRC-PM patients who are submitted to local treatments or just chemotherapy using clinical data based on "real world" setting than randomized controlled trial. The purpose of this dual-center retrospective study is to explore the factors that affect the prognosis of patients with CRC-PM, and determine the role of local intervention in the management of colorectal lung metastases through propensity score matching analyses.

**Patients And Methods**

**Patients**

All cases of CRC-PM between January 2009 to July 2019 from two institutions (The Third Affiliated Hospital, Sun Yat-Sen University and the Forth Affiliated Hospital, Henan University of Science and Technology) were retrospectively investigated. Following the inclusion criteria: 1) The primary site was diagnosed as colorectal adenocarcinoma through colonoscopy biopsy or pathological examination after surgery. 2) Pulmonary metastases from CRC were confirmed by Chest radiographs, CT or PET-CT at the first diagnosis of CRC (synchronous) or the following examination (metachronous). Exclusion criteria: 1) Unresectable extrapulmonary metastases were discovered at the diagnosis of CRC-PM; 2) Other malignancies were diagnosed. 3) Patients who have poor performance status (like cardiopulmonary failure) were diagnosed before CRC. 4) Patients who did not take any treatments for CRC because of other reasons (financial problem, etc.).

Clinical information about CRC-PM was extracted, including: patient demographics, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), location, histology and surgery of primary tumor, diagnosis time, maximum diameter, treatment, number and distribution of pulmonary metastases, extrapulmonary metastases, chemotherapy history, the level of CEA and Carbohydrate antigen199 (CA19-9) at the first diagnosis of CRC-PM, disease free interval (DFI, time between first diagnosis of CRC and CRC-PM), date of death or last follow-up visit.

According to the treatment methods of lung metastases, patients were divided into two groups. Local intervention group (Group-LI, n = 39), resection of lung metastases (lung wedge resection, lobectomy, etc.), radiofrequency ablation (microwave, cryoablation, etc.), or targeted radiotherapy, on the basis of chemotherapy; chemotherapy group (Group-Chem, n = 80), who received systemic chemotherapy only (XELOX, FOLFOX, FOLFIRI, and Xeloda single-agent chemotherapy).

**Outcome Evaluation**

Overall survival (OS) and progression-free survival (PFS) were assessed by the time from the first discovery of CRC-PM to the death or progression. The last follow-up date was December 31, 2019. Follow-up methods include:
outpatient follow-up, inpatient follow-up, telephone follow-up. For patients who are still alive or lost to follow-up, the survival duration was evaluated by the examination of the last follow-up.

**Statistical Analyses**

Differences between proportions were evaluated using the Chi-square test. Kaplan-Meier method was used for survival analysis, log-rank test was used for univariate analysis, and COX proportional hazard model was used for multivariate analysis. \( P < 0.05 \) was considered statistically significant. Statistical analysis was performed by SPSS 25.0 software (IBM Corp. USA).

Propensity score matching analyses (PSM) were performed between Group-LI and Group-Chem. The matching factors for the two groups were gender, age, staging of primary lesions at first diagnosis, pathology of primary lesions, synchronous or metachronous lung metastases, number and size of pulmonary metastases, liver, and other extrapulmonary metastases, CEA, CA19-9 and DFI.

### Results

**Patient Characteristics**

A total of 119 patients was included in the retrospective analysis (Table 1). The number of patients with CRC-PM from rectal cancer (51.1%) is approximately equal to that derived from the colon (50.9%). Metachronous pulmonary metastases have a higher proportion than synchronous metastases. 22.69% of patients had liver metastases before lung metastases were detected, who had been treated with local control (radical surgery or radiofrequency ablation) for hepatic lesions. Patients were divided into two groups: Group-LI was comprised of 39 patients who had taken local treatments for CRC-PM (21 of them were treated by pulmonary wedge resection, 8 patients received lobectomy, 6 patients submitted to cryoablation and 4 patients received targeted radiotherapy for lung metastases). There were no severe complications and deaths in Group-LI after local treatments were performed. Group-Chem included 80 patients submitted to only systemic chemotherapy (43 patients received oxaliplatin-containing doublet, 33 patients received irinotecan-based chemotherapy and 5 patients received fluoropyrimidine-based chemotherapy).

| Gender | N | 3 year-OS | 5 year-OS | HR | 95% CI | P   |
|--------|---|-----------|-----------|----|--------|-----|
| Male   | 62 | 50.3%     | 45.3%     |    |        |     |
| Female | 57 | 44.1%     | 39.7%     | 1.223 | 0.701-2.133 | 0.479 |

| Age | N | 3 year-OS | 5 year-OS | HR | 95% CI | P   |
|-----|---|-----------|-----------|----|--------|-----|
| \( \leq 60 \) years old | 66 | 51.2%     | 42.8%     |    |        |     |
| > 60 years old | 53 | 51.9%     | 35.7%     | 1.285 | 0.739-2.236 | 0.373 |

| ECOG-PS | N | 3 year-OS | 5 year-OS | HR | 95% CI | P   |
|---------|---|-----------|-----------|----|--------|-----|
| Location | Count | Percentage (Overall) | Percentage (Matched) | OR (95% CI) | P-value |
|----------|-------|----------------------|----------------------|-------------|---------|
| Colon    | 53    | 50.9%                | 37.0%                | 1.148       | 0.574–2.297 | 0.696 |
| Rectum   | 66    | 51.1%                | 41.5%                | 0.879       | 0.504–1.534 | 0.651 |
| Staging  |       |                      |                      |             |         |       |
| I        | 6     | 62.5%                | 41.7%                |             |         |       |
| II       | 25    | 67.4%                | 44.9%                | 1.150       | 0.267–4.964 | 0.851 |
| III      | 52    | 51.8%                | 35.9%                | 1.845       | 0.508–6.709 | 0.352 |
| IV       | 36    | 40.5%                | 24.0%                | 2.368       | 0.636–8.823 | 0.199 |
| Pathology|       |                      |                      |             |         |       |
| Low grade| 12    | 69.8%                | 69.8%                |             |         |       |
| Intermediate grade | 94 | 53.8%                | 37.2%                | 2.626       | 0.801–8.612 | 0.111 |
| High grade| 13 | 13.0%                | 0                    | 5.726       | 1.478–22.185 | 0.012 |
| Diagnosis of PM | | | | | | |
| Synchronous | 25 | 59.0%                | 39.3%                |             |         |       |
| Metachronous | 94 | 49.0%                | 38.8%                | 1.421       | 0.689–2.930 | 0.339 |
| Number of PM | | | | | | |
| ≤ 5 | 87 | 44.4%                | 41.9%                |             |         |       |
| > 5 | 32 | 69.7%                | 37.7%                | 0.585       | 0.300–1.143 | 0.113 |
| Sizes of PM | | | | | | |
| ≤2 cm | 88 | 47.6%                | 38.6%                |             |         |       |
|                          | >2 cm | 31 | 60.0% | 42.7% | 0.893 | 0.481–1.655 | 0.718 |
|--------------------------|-------|----|-------|-------|-------|-------------|-------|
|                          | DFI   |    |       |       |       |             |       |
| ≤12months                | 58    | 56.9% | 46.2% |       |       |             |       |
| >12months                | 61    | 45.8% | 34.9% | 1.431 | 0.820–2.497 | 0.205 |
| Distribution of PM       |       |     |       |       |       |             |       |
| Unilateral               | 41    | 70.0% | 48.4% |       |       |             |       |
| Bilateral                | 78    | 42.0% | 35.4% | 2.442 | 1.248–4.778 | 0.009 |
| Liver metastasis         |       |     |       |       |       |             |       |
| No                       | 92    | 58.1% | 49.1% |       |       |             |       |
| Yes                      | 27    | 22.6% | 0     | 2.126 | 1.151–3.929 | 0.014 |
| Extrapulmonary metastasis|       |     |       |       |       |             |       |
| No                       | 73    | 58.2% | 40.5% |       |       |             |       |
| Yes                      | 46    | 38.6% | 38.6% | 1.539 | 0.882–2.686 | 0.126 |
| CEA                      |       |     |       |       |       |             |       |
| ≤5 ng/ml                 | 55    | 74.3% | 66.7% |       |       |             |       |
| >5 ng/ml                 | 64    | 28.4% | 0     | 4.267 | 2.211–8.234 | 0.001 |
| CA19-9                   |       |     |       |       |       |             |       |
| ≤35 U/ml                 | 74    | 64.8% | 53.3% |       |       |             |       |
| >35 U/ml                 | 45    | 28.5% | 18.3% | 2.812 | 1.609–4.915 | 0.001 |
| Treatment for PM         |       |     |       |       |       |             |       |
| Local therapy            | 39    | 81.6% | 65.4% |       |       |             |       |
| Chemotherapy             | 80    | 32.2% | 23.9% | 5.871 | 2.712–12.712 | 0.001 |
Clinical Outcomes

66 patients were still alive during a median follow-up time of 36.1 months and the 3-year overall survival rate was 51.2%, and the 5-year overall survival rate was 39.7%. The 3-year progression-free survival rate was 32.7%, and the 5-year progression-free survival rate was 17.8%. In univariate analysis, the median OS was 30.5 months for patients with low tumor grade CRC, 20.9 months for patients with moderately differentiated tumor and 10.1 months for patients with high grade (low grade vs. intermediate grade, P = 0.111; low grade vs. high grade, P = 0.012). The survival duration was longer in patients with unilateral CRC-PM in those with bilateral lung metastases (27.7 months vs. 20.1 months, P = 0.009). The 3-year overall survival rates of patients who had liver metastases before lung metastases were detected was higher than those who had not (58.1% vs. 22.6%, P = 0.014). The 3-year and 5-year overall survival rates of Group-LI were 81.6% and 65.4%, higher than those of Group-Chem were 32.2% and 23.9% (P < 0.001). The gender, age, location of primary lesions, AJCC staging of first diagnosis of colorectal cancer, synchronous or metachronous lung metastases, the number and size of lung metastases, other extrapulmonary metastases, DFI was not found to be related to the overall survival rate of the patients (Table 1). The existence of extrapulmonary metastases, treatments of lung metastases, the level of CEA and CA19-9 were related to the progression-free survival of patients (Table 2).

Table 2

| Characteristics of 119 patients with CRC-PM and univariate analyses of predictive factors for PFS. |
|---------------------------------------------------|
| N | 3 year-PFS | 5 year-PFS | HR | 95%CI | P |
|---|---|---|---|---|---|
| Gender | | | | | |
| Male | 62 | 37.9% | 21.6% | | |
| Female | 57 | 26.1% | 13.3% | 1.320 | 0.841-2.073 | 0.228 |
| Age | | | | | |
| ≤ 60 years old | 66 | 37.9% | 22.4% | | |
| > 60 years old | 53 | 29.5% | 12.3% | 1.502 | 0.958-2.355 | 0.076 |
| ECOG-PS | | | | | |
| 0-1 | 97 | 31.4% | 16.3% | | |
| ≥2 | 22 | 33.8% | 19.0% | 0.884 | 0.562-1.390 | 0.594 |
| Location | | | | | |
| Colon | 53 | 37.8% | 19.9% | | |
| Rectum | 66 | 18.7% | 9.3% | 1.278 | 0.723-2.257 | 0.399 |
| Staging | | | | | |
| I     | 6    | 62.5% | 41.7% |
|-------|------|-------|-------|
| II    | 25   | 34.8% | 26.1% |
| III   | 52   | 32.1% | 19.3% |
| IV    | 36   | 26.6% | 0     |
| Pathology |      |       |       |
| Low grade | 12   | 50.0% | 40.0% |
| Intermediate grade | 94   | 32.5% | 14.9% |
| High grade | 13   | 0     | 0     |
| Diagnosis of PM |      |       |       |
| Synchronous | 25   | 51.3% | 17.1% |
| Metachronous | 94   | 27.7% | 17.4% |
| Number of PM |      |       |       |
| ≤ 5   | 87   | 29.2% | 23.8% |
| > 5   | 32   | 43.8% | 9.7%  |
| Sizes of PM |      |       |       |
| ≤2 cm | 88   | 25.6% | 15.3% |
| >2 cm | 31   | 43.5% | 22.4% |
| DFI |      |       |       |
| ≤12months | 58   | 33.4% | 15.2% |
| >12months | 61   | 32.4% | 21.6% |
| Distribution of PM |      |       |       |
| Unilateral | 41   | 52.2% | 23.2% |
|                | n   | 20.3% | 15.2% | 1.629 | 0.987-2.688 | 0.056 |
|----------------|-----|-------|-------|-------|--------------|-------|
| **Liver metastasis** |     |       |       |       |              |       |
| No             | 92  | 37.4% | 20.3% |       |              |       |
| Yes            | 27  | 14.7% | 0     | 1.517 | 0.885-2.600  | 0.130 |
| **Extrapulmonary metastasis** |     |       |       |       |              |       |
| No             | 73  | 43.3% | 24.4% |       |              |       |
| Yes            | 46  | 16.8% | 8.4%  | 1.965 | 1.248-3.093  | 0.004 |
| **CEA**        |     |       |       |       |              |       |
| ≤5 ng/ml       | 55  | 49.4% | 31.7% |       |              |       |
| >5 ng/ml       | 64  | 16.3% | 0     | 2.841 | 1.731-4.662  | 0.001 |
| **CA19-9**     |     |       |       |       |              |       |
| ≤35 U/ml       | 74  | 41.7% | 21.3% |       |              |       |
| >35 U/ml       | 45  | 13.7% | 13.7% | 1.867 | 1.160-3.005  | 0.010 |
| **Treatment for PM** |     |       |       |       |              |       |
| Local therapy  | 39  | 75.5% | 42.0% |       |              |       |
| Chemotherapy   | 80  | 12.2% | 4.9%  | 5.281 | 2.922-9.544  | 0.001 |

Multivariate analysis showed that the treatment method of lung metastases and the CEA level at the first diagnosis of lung metastases were independent prognostic factors that associated with both OS and PFS times of CRC-PM patients (Table 3,4).
### Table 3
Multivariable Cox regression for OS of patients with CRC-PM

| Factors                     | P   | HR  | 95%CI      |
|-----------------------------|-----|-----|------------|
| Treatment for PM            |     |     |            |
| Local therapy               | 0.004 | 4.07 | 1.566 10.578 |
| Chemotherapy                |     |     |            |
| CEA ≤5 ng/ml                | < 0.001 | 3.924 | 1.845 8.344 |
| CEA > 5 ng/ml               |     |     |            |
| CA19-9 ≤35 U/ml             | 0.584 | 1.204 | 0.62 2.336 |
| CA19-9 > 35 U/ml            |     |     |            |
| Liver metastasis            |     |     |            |
| No                          | 0.234 | 1.459 | 0.783 2.719 |
| Yes                         |     |     |            |
| Extrapulmonary metastasis   |     |     |            |
| No                          | 0.267 | 0.693 | 0.362 1.324 |
| Yes                         |     |     |            |
| Number of PM                |     |     |            |
| ≤5                          | 0.098 | 0.537 | 0.257 1.123 |
| > 5                         |     |     |            |
| Pathology                   |     |     |            |
| Low grade                   |     |     |            |
| Intermediate grade          | 0.852 | 0.887 | 0.25 3.141 |
| High grade                  | 0.443 | 1.832 | 0.39 8.604 |
| Distribution of PM          |     |     |            |
| Unilateral                  | 0.755 | 1.135 | 0.513 2.509 |
| Bilateral                   |     |     |            |

### Table 4
Multivariable cox regression for PFS of patients with CRC-PM

| Factors       | P   | HR  | 95%CI      |
|---------------|-----|-----|------------|
| Local therapy |     |     |            |
| Treatment for PM | Chemotherapy | < 0.001 | 5.132 | 2.414 | 10.909 |
|------------------|--------------|---------|-------|-------|--------|
| CEA              | ≤5 ng/ml     | 0.007   | 2.336 | 1.267 | 4.310  |
|                  | > 5 ng/ml    |         |       |       |        |
| CA19-9           | ≤35 U/ml     | 0.467   | 1.246 | 0.690 | 2.250  |
|                  | > 35 U/ml    |         |       |       |        |
| Liver metastasis | No           | 0.824   | 1.069 | 0.593 | 1.926  |
|                  | Yes          |         |       |       |        |
| Extrapulmonary   | No           | 0.545   | 1.185 | 0.684 | 2.051  |
| metastasis       | Yes          |         |       |       |        |
| Sizes of PM      | ≤2 cm        | 0.308   | 0.747 | 0.426 | 1.309  |
|                  | > 2 cm       |         |       |       |        |
| Pathology        | Low grade    |         |       |       |        |
|                  | Intermediate grade | 0.756 | 0.872 | 0.367 | 2.073 |
|                  | High grade   | 0.834   | 0.873 | 0.246 | 3.102  |
| Distribution of PM | Unilateral | 0.255   | 0.678 | 0.347 | 1.324  |
|                  | Bilateral    |         |       |       |        |
| Staging          | I            |         |       |       |        |
|                  | II           | 0.399   | 1.743 | 0.479 | 6.341  |
|                  | III          | 0.609   | 1.393 | 0.391 | 4.967  |
|                  | IV           | 0.250   | 2.217 | 0.571 | 8.602  |
| Diagnosis of PM  | Synchronous  |         |       |       |        |
|                  | Metachronous | 0.190   | 1.591 | 0.794 | 3.189  |
Propensity score matching analyses

There were significant differences in age, distribution of CRC-PM, extrapulmonary metastasis, the levels of CEA, CA19-9 between Group-LI and Group-Chem. The patients in the Group-LI were younger and the majority of them had unilateral lung metastases. Few of them had extrapulmonary metastasis from CRC and increase level of CEA or CA19-9. The five factors were included in the propensity score, and the prognosis comparison between 2 groups was performed after matching (Table 5). The 3-year overall survival rate of the Group-Chem (n = 24) and the Group-LI (n = 24) were 45.1% and 75.2% (HR = 3.304, P = 0.022, Fig. 1). The 3-year progression-free survival rate was 68.4% in Group-LI and 13.0% in Group-Chem (HR = 4.029, P = 0.001, Fig. 2).

Table 5
Characteristics of CRC-PM patients enrolled in study before and after PSM

|                  | Before PSM |       |       | After PSM |       |       |
|------------------|------------|-------|-------|-----------|-------|-------|
|                  | Group-LI   | Group-Chem | P | Group-LI   | Group-Chem | P |
|                  | (N = 39)   | (N = 80) |     | (N = 24) | (N = 24) |     |
| Gender           | Male       | 23    | 39   | 0.295     | 9       | 15   | 0.083 |
|                  | Female     | 16    | 41   |           | 15      | 9    |       |
| Age              | ≤60 years old | 27   | 39   | 0.035     | 16      | 16   | 1.000 |
|                  | > 60 years old | 12   | 41   |           | 8       | 8    |       |
| ECOG-PS          | 0–1        | 35    | 62   | 0.173     | 22      | 17   | 0.139 |
|                  | ≥2         | 4     | 18   |           | 2       | 7    |       |
| Pathology        | Low grade  | 7     | 5    | 0.118     | 3       | 4    | 0.197 |
|                  | Intermediate grade | 29  | 65   |           | 18      | 20   |       |
|                  | High grade | 3     | 10   |           | 3       | 0    |       |
| Diagnosis of PM  | Synchronous | 10   | 15   | 0.386     | 4       | 7    | 0.492 |

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| Distribution of PM | Metachronous | 30 | 50 | 20 | 15 | 0.773 |
|--------------------|--------------|----|----|----|----|-------|
| Unilateral         | 26           | 15 | <0.001 | 12 | 11 |       |
| Bilateral          | 13           | 65 | 12 | 13 |   |       |
| Number of PM       | ≤5           | 25 | 62 | 0.122 | 18 | 14 | 0.221 |
| > 5                | 14           | 18 | 6  | 10 |   |       |
| Sizes of PM        | ≤2 cm        | 27 | 61 | 0.413 | 19 | 21 | 0.439 |
| > 2 cm             | 12           | 19 | 5  | 3  |   |       |
| DFI                | ≤12 months   | 18 | 40 | 0.694 | 15 | 13 | 0.558 |
| > 12 months        | 21           | 40 | 9  | 11 |   |       |
| liver metastasis   | No           | 32 | 60 | 0.389 | 21 | 18 | 0.460 |
|                     | Yes          | 7  | 20 | 3  | 6  |       |
| Extrapulmonary     | No           | 32 | 41 | 0.001 | 15 | 21 | 0.096 |
|                     | Yes          | 7  | 39 | 9  | 3  |       |
| CEA                | ≤5 ng/ml     | 26 | 29 | 0.002 | 14 | 13 | 0.771 |
|                     | > 5 ng/ml    | 13 | 51 | 10 | 11 |       |
| CA19-9             | ≤35 U/ml     | 33 | 41 | <0.001 | 22 | 19 | 0.413 |
|                     | > 35 U/ml    | 6  | 39 | 2  | 5  |       |

**Discussion**

Colorectal cancer is still one of the leading causes of cancer-related death globally. For decades, although the wide application of early screening and the innovation of diagnosis and therapies have made it possible for patients with CRC in early stage to receive proper and effective treatment, how to improve the survival of patients with advanced CRC remains a problem. This study aimed to collect clinical data generated in our clinical
intervention group had a better prognosis than the chemotherapy-only group, suggesting that although...
advanced colorectal cancer should be treated as systemic diseases, local intervention of the metastases may good for controlling tumors and improving the survival of patients. For these selected patients, aggressive intervention could improve the 3-years OS and PFS.

There were some limitations in our research. Firstly, molecular markers related to the prognosis of patients were not included in retrospective analysis because they were not routinely tested until the last few years. Secondly, the impact of mediastinal and hilar lymph node metastases was not discussed because it had not been adopted as a routinely procedure during surgical resection of lung metastases in our center. Furthermore, there could be selection bias due to small sample of patients from two institutions. Nevertheless, our research provides evidence suggesting that local treatments of pulmonary metastases could improve survival of CRC-PM patients.

A randomized controlled study carrying out in Europe called PulMiCC trial, which explores whether local treatment benefit survival of CRC-PM, by comparing the overall survival of patients who receive either surgery or continued active monitoring[33]. This experiment is expected to provide strong evidence for resection of lung metastases.

## Conclusion

For patients with lung metastasis from colorectal cancer, the level of CEA at the first diagnosis of lung metastasis and local treatments for lung metastases were independent predictors of prognosis. After propensity matching score analyses, our data demonstrated that local interventions could improve the survival of patients with CRC-PM.

## Abbreviations

CRC
colorectal cancer; CRC-PM:Pulmonary metastases from colorectal cancer; Group-LI:Local intervention combined with chemotherapy group; Group-Chem:Chemotherapy group; OS:Overall survival; PFS:Progression-free survival; CEA:Carcinoembryonic antigen; CT:Computed tomography; ECOG-PS:Eastern cooperative oncology group performance status; CA19-9:Carbohydrate antigen199; DFI:Disease free interval; PSM:Propensity score matching analyses.

## Declarations

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### Author contributions

B.W. and H.W. designed the research. Z.C., Q.W., X.Y., X.Y., P.L., T.C., J.F., Z.Z., and J.X. collected the data. Z.C., Q.W., and X.Y. analyzed the data. B.W., and Z.C. wrote the paper. H.W. and B.W. revised the manuscript. All authors have read and approved the final submitted manuscript.

### Competing interests
The authors declare that they have no competing interests.

**Consent for publication**

Not applicable.

**Ethics approval and consent to participate**

This study was approved by the ethics committee of our hospital and was in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Availability of data and materials**

The datasets used during the current study are available from the corresponding author on reasonable request.

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Figure 1
Kaplan-Meier curves of survival duration for Group-LI and Group-Chem. (a: OS before PSM, b: OS after PSM, c: PFS before PSM, d: PFS after PSM)
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Kaplan-Meier curves of survival duration for Group-LI and Group-Chem. (a: OS before PSM, b: OS after PSM, c: PFS before PSM, d: PFS after PSM)