Anatomical Resection Improves Disease-Free Survival After Lung Metastasectomy of Colorectal Cancer

**Purpose:** This study aimed to evaluate the role of anatomical resection (AR) in lung metastasectomy (LM) of colorectal cancer (CRC) and to investigate clinically relevant prognostic factors.

**Patients and Methods:** The medical records of 350 consecutive patients who underwent LM of CRC from 2011 to 2019 were reviewed. The patients were designated into AR group (lobectomy and segmentectomy), and non-anatomical resection (NAR) group (wedge resection), respectively. Kaplan–Meier method was used to analyze disease-free survival (DFS), pulmonary-specific disease-free survival (PDFS) and overall survival (OS). Cox proportional hazards regression model was performed to analyze the factors associated with DFS, PDFS and OS.

**Results:** A total of 92 (31.2%) patients were enrolled in AR group and 203 (68.8%) in non-anatomical resection (NAR) group. AR significantly improved the 3-year DFS (64.1% vs 46.8%, HR 0.587, 95% CI 0.397–0.867, P = 0.007) and PDFS (75.0% vs 60.1%, HR 0.565, 95% CI 0.356–0.899, P = 0.016) compared with NAR. However, the extent of resection did not significantly impact the 3-year OS (AR 92.4% vs NAR 85.7%, HR 0.511, 95% CI 0.224–1.165, P = 0.110). In multivariate analysis, AR was identified as a protective factor for DFS (HR 0.576, 95% CI 0.356–0.934, P = 0.025) and PDFS (HR 0.631, 95% CI 0.409–0.973, P = 0.037). Preoperative abnormal CA19-9 was identified as the only prognostic factor for OS.

**Conclusion:** AR was superior to NAR for DFS and PDFS after LM from CRC.

**Keywords:** pulmonary metastasis, lobectomy, wedge resection, prognosis

**Introduction**

The most common extra-abdominal metastasis of colorectal cancer (CRC) was lung metastasis, which initially appears in approximately 24.5% to 29.2% of metastatic CRC. It has been widely acknowledged that lung metastasectomy (LM) could provide survival benefits for selected CRC patients with limited metastases. However, it remains unclear whether non-anatomical resections (NAR) or anatomical resections (AR) provide better outcomes after pulmonary metastasectomy of CRC.

Owing to high rate of lung recurrence, NAR (wedge resection) is preferred by many specialists for pulmonary parenchymal sparing and preservation of pulmonary function, which allows repeated resections. Indeed, repeated lung resection can be performed safely without increasing post-operative morbidity and can lead to good outcomes. However, NAR may be associated with increased risk of local...
recurrence. On the other hand, AR (segmentectomy or lobectomy) may seem to be so aggressive in most cases that it becomes a less dominant surgical approach in clinical practice. Intriguingly, some recent studies have reported that AR could be associated with lower recurrence rate and provide better survival outcomes after LM of CRC compared with NAR, especially in CRC patients harboring KRAS mutations, while no evidence suggesting the opposite conclusion has been reported. To date, the evidence remains too limited and lacking of high-quality clinical trials, the debate about the extent of resection in LM is still out there, which calls for more related data to answer the question.

The objective of this study was to compare the clinical outcomes between CRC patients who received NAR and AR in LM, and to investigate the factors associated with survival outcomes following LM of CRC.

Materials and Methods
Patients
We retrospectively reviewed the medical records of 350 consecutive patients who underwent LM for CRC with curative intent in Zhongshan Hospital, Fudan University from January 2011 to December 2019. Inclusion criteria of this study were as follows: the pulmonary lesions were accessed to be metastases from CRC and confirmed by at least one pathologist, the LM was performed with curative intent. The exclusion criteria included other extrahepatic metastases, palliative resection, previous history of other malignant tumors, mutation of BRAF, ablation or other palliative local treatment of the metastases, and prior LM received before the first visit.

According to the extent of resection, AR group was defined as lobectomy and segmentectomy, while NAR group was defined as wedge resection. Written informed consent was obtained from all patients before the start of the study. This study was approved by the Institutional Ethics Committee of Zhongshan Hospital, Fudan University, and was conducted in accordance with the Declaration of Helsinki.

Pulmonary Surgery
Surgical approach was determined by the thoracic surgeons based on the localization of the identified lesions and the principle of achieving an R0 resection. Specifically, wedge resection was preferentially adopted under the premise of R0 resection could be achieved. Segmentectomy and lobectomy were performed only in cases with central or large lesions that were not accessible by wedge resection.

Hilar or mediastinal lymphadenectomy was not routinely performed in our practice. In general, chest CT and PETCT scan were routinely used to evaluate the lymph node metastases prior to LM. Lymphadenectomy was performed in the presence of suspicious lymph nodes on radiographic imaging.

Follow-Up
The patients were followed up according to clinical practice guidelines. The following information was recorded: age,
sex, location and staging of primary lesion, disease-free interval (DFI) length, preoperative carcino-embryogenic antigen (CEA) and cancer antigen 19-9 (CA19-9) levels, history of liver metastases, surgical approach of LM, dissection of lymph nodes, KRAS, NRAS and BRAF statues, over all survival (OS), disease-free survival (DFS) and pulmonary-specific disease-free survival (PDFS).

The KRAS/NRAS/BRAF mutation status was preferentially reviewed in pulmonary samples obtained from surgical specimens, unless the status was just detected in the primary tumor. AmoyDx™ KRAS/NRAS/BRAF Mutations Detection Kit (AmoyDx, Xiamen, China) was used to detect KRAS/NRAS/BRAF mutation status, and the detection process had been described in our previous study.19 Considering the combination of liver metastasis often occurred in our CRC patients with lung metastasis, the DFI was precisely defined in three different ways: DFI-1 was defined as the interval between the primary CRC surgery and the diagnosis of either a thoracic or a liver metastasis via imaging; DFI-2 was the interval between the primary CRC surgery and the diagnosis of a thoracic

| Table 1 Baseline Characteristics of Patients (n = 295) |
|----------------|----------------|----------------|----------------|
|                | NAR (n = 203) n (%) | AR (n = 92) n (%) | P value |
| Age (years)    |                |                |          |
| ≤60            | 99 (48.8)      | 39 (42.4)      | 0.309   |
| >60            | 104 (51.2)     | 53 (57.6)      |         |
| Sex            |                |                | 0.680   |
| Male           | 133 (65.5)     | 58 (63.0)      |         |
| Female         | 70 (34.5)      | 34 (37.0)      |         |
| Location of primary tumor | | | |
| Colon          | 70 (34.5)      | 42 (45.7)      | 0.067   |
| Rectum         | 133 (65.5)     | 50 (54.3)      |         |
| pT stage of primary tumor | | | |
| 1–2            | 28 (13.8)      | 9 (9.8)        | 0.224   |
| 3–4            | 127 (62.6)     | 53 (57.6)      |         |
| Unknown        | 48 (23.6)      | 30 (32.6)      |         |
| pN stage of primary tumor | | | |
| 0              | 57 (28.1)      | 24 (26.1)      | 0.153   |
| 1–2            | 99 (48.8)      | 37 (40.2)      |         |
| Unknown        | 47 (23.2)      | 31 (33.7)      |         |
| Lung metastases pattern | | | |
| Synchronous    | 43 (21.2)      | 79 (85.9)      | 0.153   |
| Metachronous   | 160 (78.8)     | 13 (14.1)      |         |
| DFI-1 (months) |                |                | 0.055   |
| ≤24            | 132 (65.0)     | 49 (53.3)      |         |
| >24            | 71 (35.0)      | 43 (46.7)      |         |
| Neoadjuvant therapy* | | | |
| Yes            | 22 (10.8)      | 11 (12.0)      | 0.778   |
| No             | 181 (89.2)     | 81 (88.0)      |         |
| Adjuvant therapy* | | | |
| Yes            | 125 (61.6)     | 62 (67.4)      | 0.452   |
| No             | 46 (22.7)      | 15 (16.3)      |         |
| Unknown        | 32 (15.8)      | 15 (16.3)      |         |
| Preoperative CEA (ng/mL) | | | |
| <5             | 117 (57.6)     | 42 (45.7)      | 0.143   |
| ≥5             | 60 (29.6)      | 33 (35.9)      |         |
| Unknown        | 26 (12.8)      | 17 (18.5)      |         |
| Preoperative CA19-9 (U/mL) | | | |
| <37            | 142 (70.0)     | 55 (59.8)      | 0.172   |
| ≥37            | 19 (9.4)       | 9 (9.8)        |         |
| Unknown        | 42 (20.7)      | 28 (30.4)      |         |
| Number of lung metastases | | | |
| 1              | 163 (80.3)     | 78 (84.8)      | 0.356   |
| ≥2             | 40 (19.7)      | 14 (15.2)      |         |
| Distribution of lung lesions | | | |
| Unilobar       | 177 (87.2)     | 91 (98.9)      | 0.001   |
| Bilobar        | 26 (12.8)      | 1 (1.1)        |         |
| Maximum diameter of the pulmonary lesions (cm) | | | |
| <2             | 133 (65.5)     | 34 (37.0)      | 0.000   |
| ≥2             | 70 (34.5)      | 58 (63.0)      |         |

(Continued)
metastasis via imaging. DFI-3 was the interval from the surgery of primary colorectal lesions and liver metastases, if any, to the diagnosis of a thoracic metastasis via imaging. DFS was defined as the time from the LM to the diagnosis of recurrence/metastasis or the last follow-up. PDFTS was defined as the time from the LM to lung recurrence or the last follow-up. OS was defined as the time from LM to death or the last follow-up.

**Statistical Analysis**
Statistical analysis was processed via SPSS software version 22.0. The Chi-square test and Fisher’s exact test were used for categorical data. Survival curves were estimated with Kaplan–Meier method and compared using Log rank test. Univariable and multivariable Cox proportional-hazards regression analyses were carried out to identify the prognostic factors for OS, DFS and PDFTS, respectively. All hypothesis tests were bilateral and a P-value <0.05 was considered statistically significant. The survival curve was plotted with GraphPad Prism software (Version 8.2.1).

**Results**

**Characteristics of Patients**
A total of 295 CRC patients were enrolled in this study. Of the 295 patients, 203 (68.8%) received NAR and 92 (31.2%) received AR, including 73 (24.7%) received lobectomy and 19 (6.4%) received segmentectomy (Figure 1). The maximum diameter of pulmonary lesions of the AR group was significantly greater than that of the NAR group (P = 0.000). As for lymphadenectomy, it was performed in more patients in the AR group than in the NAR group (79.3% vs 21.2%, P = 0.000), which was attributed to the difficulty of achieving complete resection or sampling of lymph nodes via wedge resection. However, no significant difference was observed in lymph node metastasis between the two groups. Bilobar resection was performed in 26 (12.8%) patients in the NAR group and 1 (1.1%) in the AR group (P = 0.001).

The KRAS/NRAS/BRAF status was reviewed in 248 patients, of which, 232 was reviewed in pulmonary specimens and 97 in primary specimens. No significant difference was observed in other parameters, and all details are listed in Table 1.

**Disease-Free Survival**
With a median follow-up of 34.6 months overall, recurrence and metastasis were observed in 37 (40.2%) patients in the AR group and 115 (56.7%) in the NAR group. The DFS was significantly improved in patients who underwent AR (median DFS not reached) when compared to who received NAR (median DFS 26.2 months, 95% CI 20.9–31.6) (Figure 2A.
Log rank $P = 0.009$). The 3-year DFS of the AR and NAR group were 64.1% and 46.8%, respectively (HR = 0.587, 95% CI 0.397–0.867, $P = 0.007$). In univariate analysis, DFS was associated with DFI-3, preoperative CA19-9 level, maximum diameter of the pulmonary lesions, the history of liver metastasis and type of LM, but not some previously reported factors, such as RAS status or preoperative CEA level. In multivariate analysis, AR was the only prognostic factor of better outcome for patients (HR = 0.576, 95% CI 0.356–0.934, $P = 0.025$), while the history of liver metastasis was an independent prognostic factor of worse outcome (HR = 1.987, 95% CI 1.330–2.969, $P = 0.001$) (Table 2).

**Pulmonary-Specific Disease-Free Survival**

During follow-up, 27 (29.3%) patients in the AR group and 87 (42.9%) in the NAR group experienced pulmonary recurrence. The PDFS was significantly improved in the AR group compared with the NAR group (Log rank $P = 0.025$), with the corresponding 3-year PDFS being 75.0% and 60.1%, respectively (HR 0.565, 95% CI 0.356–0.899, $P = 0.016$). In univariate and multivariate analyses, PDFS was associated with the history of liver metastasis and type of LM. AR was an independent prognostic factor of prolonged PDFS (HR = 0.631, 95% CI 0.409–0.973, $P = 0.037$). The history of liver metastasis was an independent prognostic factor of worse outcome (HR = 1.563, 95% CI 1.048–2.332, $P = 0.028$) (Table 3).

**Overall Survival**

A total of 43 deaths occurred during follow-up, including 10 (10.9%) in the AR group and 33 (16.3%) in the NAR group. The extent of resection in LM did not significantly affect the OS (Log rank $P = 0.222$). The 3-year OS in the AR group and the NAR group were 92.4% and 85.7%, respectively (HR = 0.511, 95% CI 0.224–1.165, $P = 0.110$). In univariate analysis, preoperative abnormal CA19-9 level, KRAS status, the history of liver metastasis and pulmonary lymph node metastasis were significantly associated with worse OS, while in multivariate analysis, only preoperative abnormal CA19-9 level was identified (HR = 3.522, 95% CI 1.430–8.678, $P = 0.006$) (Table 4).

**Discussion**

In the era of precision therapy, there has been much debate on whether AR or NAR in LM of CRC should be endorsed

### Table 2 Uni- and Multivariate Analyses of DFS

| Age (years) | ≤60/>60 | 1.338 (0.973–1.840) | 0.073 | / | / |
| Sex | Male/Female | 1.345 (0.949–1.905) | 0.096 | / | / |
| Location | Rectum/Colon | 0.855 (0.619–1.182) | 0.344 | / | / |
| T stage | 3–4/1–2 | 0.989 (0.610–1.602) | 0.963 | / | / |
| N stage | 1–2/0 | 1.160 (0.796–1.691) | 0.440 | / | / |
| Lung metastases pattern | Synchronous/Metachronous | 1.187 (0.807–1.746) | 0.383 | / | / |
| DFI-1 (months) | ≤24/>24 | 1.349 (0.964–1.886) | 0.081 | / | / |
| DFI-2 (months) | ≤24/>24 | 1.375 (0.993–1.904) | 0.055 | / | / |
| DFI-3 (months) | ≤24/>24 | 1.503 (1.071–2.109) | 0.018 | 1.418 (0.941–2.138) | 0.095 |
| CEA level (ng/mL) | ≥5/<5 | 0.955 (0.662–1.378) | 0.808 | / | / |
| CA19-9 level (U/mL) | ≥37/<37 | 1.780 (1.075–2.948) | 0.025 | 1.501 (0.894–2.527) | 0.127 |
| Number of lung metastases | >1/1 | 1.369 (0.931–2.014) | 0.111 | / | / |
| Distribution of lung lesions | Bilobar/Unilobar | 1.257 (0.748–2.111) | 0.388 | / | / |
| Maximum diameter of the pulmonary lesions (cm) | ≥2/<2 | 0.648 (0.466–0.902) | 0.010 | 1.106 (0.721–1.695) | 0.645 |
| Metastasis of lung lymph node | Yes/No | 1.255 (0.448–3.510) | 0.666 | / | / |
| Liver metastases | Yes/No | 2.107 (1.500–2.960) | 0.000 | 1.987 (1.330–2.969) | 0.001 |
| Type of resection | AR/NAR | 0.613 (0.423–0.889) | 0.010 | 0.576 (0.356–0.934) | 0.025 |
| Neoadjuvant therapy | Yes/No | 1.544 (0.982–2.428) | 0.060 | / | / |
| Adjuvant therapy | Yes/No | 0.773 (0.529–1.129) | 0.183 | / | / |
| KRAS status | Mutation/Wild type | 1.152 (0.810–1.640) | 0.431 | / | / |
| NRAS status | Mutation/Wild type | 0.948 (0.387–2.321) | 0.908 | / | / |

**Abbreviations:** HR, hazard ratio; CI, confidence interval; DFI, disease-free interval; CEA, carcino-embryogenic antigen; CA19-9, cancer antigen 19-9; AR, anatomical resection; NAR, non-anatomical resection.
to achieve better outcomes.\textsuperscript{7,8} This study indicated that compared with NAR, AR was associated with better DFS and PDFS following LM of CRC patients, while no statistically significant difference was observed on OS between the two surgical approaches.

Several studies have compared the oncological outcomes between NAR and AR, the conclusions happened to be similar with what was found in this study.\textsuperscript{14,15} For example, Shiono et al reported that segmentectomy was superior to wedge resection for lower resection-margin recurrence rate (2.0\% vs 7.3\%, $P = 0.035$) and better 5-year OS (80.1\% vs 68.5\%).\textsuperscript{15} The GECMP-CCR study compared major resection (lobectomy and pneumonectomy) with lesser resection (wedge resection and segmentectomy), and found that major resection could improve DFS (median not reached vs 23.9 months, HR 0.5, $P < 0.001$).\textsuperscript{14} On the other hand, no direct evidence in favor of NAR on this issue has been reported as far as we know. Being different from the previous studies, the present study defined AR as lobectomy and segmentectomy, which seems more reasonable as they were performed according to anatomical structure. Although the OS of AR group was higher than that of NAR group, however, no statistical difference was reach. The short follow-up time may be one of the reasons to explain this result. In addition, not all patients received adjuvant treatment in our hospital, which may affect the prognosis of CRC patients received LM.\textsuperscript{20–23}

For whether to recommend AR or NAR in LM of CRC, the conclusion of this study, along with those of the several previous studies,\textsuperscript{14–16} kind of challenges the current practice. In such an era highly endorsing minimally invasive procedures in clinical practice, wedge resection is preferred whenever possible and has become the dominant surgical approach for pulmonary metastases of CRC, especially with video-assisted thoracoscopic surgery (VATS) being widely used, while segmentectomy and lobectomy are less frequently performed, according to the previous studies and our own experience.\textsuperscript{14–16} Moreover, less than lobectomy was also recommended by the Expert Consensus of the Society of Thoracic Surgeons, while in which, lobectomy was just occasionally indicated.\textsuperscript{17} Given the contradiction between the generally accepted concept and the findings of the previous studies, the debate on the

### Table 3 Uni- and Multivariate Analyses of PDFS

|                  | Univariate Analysis | Multivariate Analysis |
|------------------|---------------------|-----------------------|
|                  | HR (95\% CI)        | P                     |
|                  |                     | HR (95\% CI)          | P |
| Age (years)      | ≤60/>60             | 1.317 (0.912–1.902)   | 0.142 | / | / |
| Sex              | Male/Female         | 1.210 (0.813–1.802)   | 0.348 | / | / |
| Location         | Rectum/Colon        | 0.989 (0.678–1.442)   | 0.955 | / | / |
| T stage          | 3–4/1–2             | 0.876 (0.502–1.530)   | 0.643 | / | / |
| N stage          | 1–2/0               | 1.151 (0.748–1.773)   | 0.522 | / | / |
| Lung metastases  | Synchronous/Metachronous | 0.846 (0.522–1.372)  | 0.498 | / | / |
| DFI-1 (months)   | ≤24/>24             | 1.212 (0.826–1.778)   | 0.325 | / | / |
| DFI-2 (months)   | ≤24/>24             | 1.179 (0.812–1.711)   | 0.386 | / | / |
| DFI-3 (months)   | ≤24/>24             | 1.218 (0.831–1.787)   | 0.312 | / | / |
| CEA level (ng/mL)| ≥5/<5               | 0.825 (0.537–1.267)   | 0.380 | / | / |
| CA19-9 level (U/mL)| ≥37/<37        | 1.226 (0.651–2.312)   | 0.528 | / | / |
| Number of lung metastases | > 1/1              | 1.413 (0.912–2.190)   | 0.122 | / | / |
| Distribution of lung lesions | Bilobed/Unilobar | 1.331 (0.747–2.372)   | 0.332 | / | / |
| Maximum diameter of the pulmonary lesions (cm) | ≥2/<2       | 0.896 (0.619–1.303)   | 0.571 | / | / |
| Metastasis of lung lymph node | Yes/No  | 1.951 (0.681–5.587)   | 0.213 | / | / |
| Liver metastases | Yes/No             | 1.601 (1.075–2.385)   | 0.020 | 1.563 (1.048–2.332) | 0.028 |
| Type of resection | AR/NAR           | 0.612 (0.397–0.943)   | 0.026 | 0.631 (0.409–0.973) | 0.037 |
| Neoadjuvant therapy | Yes/No      | 1.610 (0.973–2.664)   | 0.064 | / | / |
| Adjuvant therapy  | Yes/No             | 0.699 (0.453–1.076)   | 0.104 | / | / |
| KRAS status      | Mutation/Wild type | 1.181 (0.790–1.765)   | 0.417 | / | / |
| NRAS status      | Mutation/Wild type | 0.971 (0.357–2.644)   | 0.955 | / | / |

**Abbreviations:** HR, hazard ratio; CI, confidence interval; DFI, disease-free interval; CEA, carcino-embryogenic antigen; CA19-9, cancer antigen 19-9; AR, anatomical resection; NAR, non-anatomical resection.
extent of resection is still out there. In this case, it is of great importance to provide more evidences on this issue to make it clear.

Based on what mentioned above, for selection of AR or NAR in clinical practice, it will be worthy to step back and go deep into the fundamentals to reconsider it. For one thing, the localization of identified pulmonary metastases basically determines whether NAR can be performed, but in fact, it is difficult to assure that all the metastases have been found during the preoperative evaluation and the surgery, especially those metastasized to the lymph nodes. For another, the possibility of complete lymph node dissection is a major difference between AR and NAR, and remains a crucial issue in decision-making. It is acknowledged that lymph node metastasis of pulmonary metastases could affect prognosis, and lymph node sampling or dissection during LM has been recommended.17

In this case, NAR giving little accessibility to perform lymph node resection, seems not appropriate enough even if it seems to be able to achieve R0 resection. Besides, our data regarding lymph node sampling have also suggested some disturbing issues of NAR. As shown in Table 1, obviously more patients in the AR group received lymph node dissection than those in the NAR group, but even with less sampling, the cases with metastasis-positive lymph nodes were still more in the NAR group than in the AR group (11.6% vs 5.5%), which kind of suggests that NAR could possibly fail to eradicate all metastasis-positive lymph nodes. Taken together, we believe that in physiologically appropriate patients, AR is a better choice for LM of CRC than NAR.

Reviewing the previous literatures, we firstly noticed that the KRAS status may be the prognostic factor of LM of CRC.24,25 As reported by a multicenter retrospective study performed by Renaud et al, segmentectomy improved both the OS and time to pulmonary recurrence in LM of CRC harboring KRAS mutations.16 In the present study, KRAS harboring KRAS mutations was found in 145 patients and NRAS mutation in 10 patients. We observed the association between KRAS mutation and OS in univariate analysis. However, multivariable analysis did not identify NRAS or KRAS status as prognosis factor of DFS, PDFS or OS.

Table 4 Uni- and Multivariate Analyses of OS

| Age (years) | ≤60/>60 | 1.273 (0.700–2.315) | 0.430 | / | / |
| Sex | Male/Female | 1.336 (0.686–2.602) | 0.394 | / | / |
| Location | Rectum/Colon | 0.684 (0.376–1.245) | 0.214 | / | / |
| T stage | 3–4/1–2 | 0.766 (0.334–1.754) | 0.528 | / | / |
| N stage | 1–2/0 | 1.438 (0.690–2.995) | 0.332 | / | / |
| Lung metastases pattern | Synchronous/Metachronous | 0.714 (0.317–1.610) | 0.417 | / | / |
| DFI-1 (months) | ≤24/>24 | 0.956 (0.518–1.763) | 0.885 | / | / |
| DFI-2 (months) | ≤24/>24 | 0.971 (0.531–1.775) | 0.981 | / | / |
| DFI-3 (months) | ≤24/>24 | 0.940 (0.510–1.733) | 0.843 | / | / |
| CEA level (ng/mL) | ≥5/<5 | 1.186 (0.579–2.430) | 0.641 | / | / |
| CA19-9 level (U/mL) | ≥37/<37 | 4.853 (2.257–10.434) | 0.000 | 3.522 (1.430–8.678) | 0.006 |
| Number of lung metastases | >1/1 | 0.871 (0.387–1.959) | 0.738 | / | / |
| Distribution of lung lesions | Bilobar/Unilobar | 0.766 (0.237–2.476) | 0.656 | / | / |
| Maximum diameter of the pulmonary lesions (cm) | ≥2/<2 | 0.974 (0.531–1.786) | 0.932 | / | / |
| Metastasis of lung lymph node | Yes/No | 3.272 (0.912–11.742) | 0.069 | / | / |
| Liver metastases | Yes/No | 1.961 (1.054–3.649) | 0.033 | 1.991 (0.855–4.637) | 0.110 |
| Type of resection | AR/NAR | 0.646 (0.318–1.310) | 0.226 | / | / |
| Neoadjuvant therapy | Yes/No | 0.551 (0.170–1.781) | 0.319 | / | / |
| Adjuvant therapy | Yes/No | 0.736 (0.360–1.507) | 0.402 | / | / |
| KRAS status | Mutation/Wild type | 2.352 (1.092–5.067) | 0.029 | 1.679 (0.696–4.051) | 0.249 |
| NRAS status | Mutation/Wild type | 0.720 (0.098–5.273) | 0.747 | / | / |

Abbreviations: HR, hazard ratio; CI, confidence interval; DFI, disease-free interval; CEA, carcino-embryogenic antigen; CA19-9, cancer antigen 19-9; AR, anatomical resection; NAR, non-anatomical resection.
Second, the DFI was a prognostic factor in some previous studies.²⁵ In this study, we calculated the DFIs using three kinds of method to explore the influence of calculation method. As a result, none of the DFIs was identified as prognostic factor in multivariable analysis. Third, the 3-year OS of all patients was 87.8%, with 92.4% in AR group and 85.7% in NAR group, which was slightly higher than previous studies.²⁷,²⁸ One reason to explain the better outcome was that the subjects in this study were highly selected. The subjects with extrahepatic metastases were excluded, and all the liver metastases received R0 resection. Another reason may be the higher proportion of adjuvant chemotherapy than previous studies.²⁷,²⁸

A few limitations must be considered when interpreting this study. Since the present study was a retrospective study with not pre-established criteria of the type of resection, a patient selection bias could not be avoided, for example, the maximum diameter of the pulmonary metastases and the dissection of lymph node. However, the outcomes of the AR group were better than those of the NAR group despite of this study. Since the present study was a retrospective study with not pre-established criteria of the type of resection, this may significantly affect the survival outcomes. However, the distribution of lung lesions did not significantly affect the survivals. With limited data and no dramatical superiority of either type of resection being reported, the research on this issue may probably remain observational on the near future, and more data need to be provided before launching a large-scale randomized controlled trial.

Conclusion
This study has provided the evidence on AR improving survival outcomes following LM in CRC patients, specifically for DFS and PDFS. However, whether AR can benefit OS remains questionable, which calls for more high-quality evidences on it.

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Disclosure
There was no financial and personal relationship with other people and organizations that could inappropriately influence this work. The authors report no conflicts of interest in this work.

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