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The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

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ORIGINAL ARTICLE

Retrospective Study

Adjuvant chemotherapy for isolated resectable colorectal lung metastasis: A retrospective study using inverse probability treatment weighting propensity analysis

Zhao Gao, Shi-Kai Wu, Shi-Jie Zhang, Xin Wang, Ying-Chao Wu, Xuan Jin

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Abstract

BACKGROUND

The benefit of adjuvant chemotherapy (ACT) for patients with no evidence of disease after pulmonary metastasis resection (PM) from colorectal cancer (CRC) remains controversial.

AIM

To assess the efficacy of ACT in patients after PM resection for CRC.

METHODS

This study included 96 patients who underwent pulmonary metastasectomy for CRC at a single institution between April 2008 and July 2023. The primary endpoint was overall survival (OS); secondary endpoints included cancer-specific survival (CSS) and disease-free survival (DFS). An inverse probability of treatment-weighting (IPTW) analysis was conducted to address indication bias. Survival outcomes compared using Kaplan-Meier curves, log-rank test, Cox regression and confirmed by propensity score-matching (PSM).

RESULTS

With a median follow-up of 27.5 months (range, 18.3-50.4 months), the 5-year OS, CSS and DFS were 72.0%, 74.4% and 51.3%, respectively. ACT had no significant effect on OS after PM resection from CRC [original cohort: P = 0.08; IPTW: P = 0.15]. No differences were observed for CSS (P = 0.12) and DFS (P = 0.68) between the ACT and non-ACT groups. Multivariate analysis showed no association of

ACT with better survival, while sublobar resection (HR = 0.45; 95%CI: 0.20-1.00, *P* = 0.049) and longer disease-free interval (HR = 0.45; 95%CI: 0.20-0.98, *P* = 0.044) were associated with improved survival.

CONCLUSION

ACT does not improve survival after PM resection for CRC. Further well-designed randomized controlled trials are needed to determine the optimal ACT regimen and duration.

Key Words: Colorectal cancer; Resection of pulmonary metastasis; Adjuvant chemotherapy; Inverse probability treatment weighting; Prognosis

Core Tip: It remains controversial whether patients who have reached no evidence disease after resection of pulmonary metastasis of colorectal cancer (CRC) can benefit from adjuvant chemotherapy (ACT). We aimed to evaluate the efficacy of ACT in patients after resection of pulmonary metastasis resection from CRC. Due to the lack of randomized prospective trials and high level evidence, our study may support valuable data support for individual participant data meta-analysis and help further research on this type of disease.

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INTRODUCTION

In 2022, colorectal cancer (CRC) became the third most common malignancy worldwide and the second leading cause of cancer-related deaths[1]. Metastasis of CRC is the primary cause of death in CRC[2,3], with a 5-year survival rate of approximately 56% for non-metastatic cases, which drops significantly once metastasis occurs[4,5]. Unlike many other cancers, metastatic CRC is often amenable to surgical intervention[6]. The lungs, following the liver, are the second most common site for CRC metastasis, accounting for 10%-15% of cases[7]. Although research on lung metastasis is limited compared to liver metastasis, patients with lung metastases generally have a better prognosis[8]. Key prognostic factors for prolonged survival include disease-free interval (DFI), tumor diameter, preoperative carcinoembryonic antigen (CEA) levels, and the number of lung metastases[9]. Despite surgery being the primary treatment for lung metastasis, with a 5-year overall survival (OS) rate of 50%, the recurrence rate remains high at 68%, predominantly in the remaining lung tissue[10].

Metastasis is the main determinant of long-term survival in CRC, responsible for 90% of tumor-related deaths[11,12]. Adjuvant therapy is intended to eliminate micro-metastases following surgery[13]; however, the role of adjuvant chemotherapy (ACT) in improving survival after resection of pulmonary metastases (PM) remains controversial[14-16]. Previous studies and meta-analyses have provided conflicting evidence regarding the benefit of ACT and perioperative chemotherapy in this setting[17,18]. This study aimed to clarify the role of ACT after lung metastasectomy in patients with CRC at our center.

MATERIALS AND METHODS

Data acquisition

The medical records were retrospectively queried to identify patients who underwent pulmonary metastasectomy for CRC at Peking University First Hospital between April 2008 to June 2023. Patients with an index pulmonary metastasectomy at an outside facility were excluded. Inclusion criteria were: (1) Histopathologically confirmed adenocarcinoma of CRC, radically resected with no signs of local recurrence; and (2) If ACT was administered after surgery for the primary lesion, the interval between the last ACT and the radical resection of lung metastases was greater than three months. Exclusion criteria were: (1) Synchronous lung metastases; and (2) Extrapulmonary metastases or multiple bilateral lung metastases that could not be resected using R0 criteria. Isolated lung metastasis was defined as a CRC lung metastasis without extrapulmonary involved. Ten patients (10.4%) underwent surgery for extrathoracic metastases (mainly liver metastases), with the last treatment for extrathoracic metastases occurring at least 3 months after the discovery of isolated lung metastases. Surgical methods for lung metastases included lobectomy and sublobar resection (wedge resection and segmentectomy). This study was approved by the Ethics Committee of the Peking University First Hospital.

Follow-up

Follow-up data were obtained through hospital record reviews and telephone contact. The final follow-up period was January 2024. OS was the primary outcome, calculated from the date of lung surgery to the date of death from any cause, with censored cases defined by the last available follow-up. Cancer-specific survival (CSS) and disease-free survival (DFS) were assessed monthly from the surgery date until tumor progression or death.

Statistical analysis

Analyses were performed with R statistical software version 4.3.2, with significance set at $P \leq 0.05$. Continuous variables were compared using Student's *t*-test, while categorical variables were assessed with the χ^2 test. Survival analysis was conducted using the Kaplan-Meier method and multivariate Cox regression. Inverse probability of treatment weighting (IPTW) was used to adjust for differences between the ACT and non-ACT groups, with weights set as the inverse of the propensity score for those receiving ACT and the inverse of (1-propensity score) for those not receiving ACT. Standardized mean differences (SMDs) were calculated to assess covariate balance post-IPTW, with SMD values less than 0.2 indicating low covariate imbalance[19]. Pseudo-data generated by IPTW increased the sample size of the original data potentially inflating statistical significance, which was mitigated by using stabilized weights[20]. Missing data ranged from 0% to 29.2%. Missing data were handled by multiple imputations using chained equations *via* the mice package in R, in which predictive mean matching was embedded with the cases (k) = 5 default[21]. Univariate analysis was performed on complete cases before imputation, while multivariate analyses included the imputed data for confounders[22]. Statistical significance was set at $P < 0.05$, and all probability values were two-tailed.

Sensitivity analysis

To address potential biases, three sensitivity analyses were conducted. First, comparisons were made between data before and after the missing-value interpolation. Second, a complete case analysis was used to replace imputed laboratory values. Third, propensity score matching analysis, an alternative to IPTW, was employed to adjust for baseline imbalances and evaluate treatment outcomes.

RESULTS

Participants

During the study period, 96 patients met the inclusion criteria, with a majority being men (n = 58; 60.4%), and a median age of 62.6 years (Table 1). Among these patients, 28 (29.2%) reported a history of tobacco use. All patients (100%) were diagnosed with lung metastases during follow-up, with a median DFI of 28.5 months. Ten patients (10.4%) had previously undergone surgery for extra-thoracic metastases, primarily liver metastases. ACT was administered to 35.4% of the patients during radical resection for isolated lung metastases (Table 1).

Table 1 Clinical, radiological, and histological characteristics of the population

Factors	Total, *n* (%)
Gender	
Male	58 (60.4)
Female	38 (39.6)
Age at CRC diagnosis	
Median (IQR)	59.7 (49.8-69.6)
Age at time of pulmonary surgery	
Median (IQR)	62.6 (53-72.2)
Access	
Open	20 (20.8)
VATS	76 (79.2)
Type of resection	
Sublobar resection	54 (56.2)
Lobectomy	42 (43.8)
Adjuvant chemotherapy for PM	
No	62 (64.6)

Yes	34 (35.4)
Primary tumor T stage	
T1 or T2	8 (11.8)
T3 or T4	60 (88.2)
Primary tumor N stage	
N0	28 (39.4)
N1 or N2	43 (60.6)
Primary tumor location	
Left colon	29 (33.0)
Right colon	17 (19.3)
Rectum	42(47.7)
Adjuvant chemotherapy for CRC	
No	30 (31.2)
Yes	66 (68.8)
CEA levels	
≤ 5 ng/mL	47 (60.3)
> 5 ng/mL	31 (39.7)
Number of metastatic lesions	
1	76 (79.2)
> 1	20 (20.8)
Tumor size (cm)	
≤ 2 cm	51 (54.8)
> 2 cm	42 (45.2)
Prior extra-thoracic metastasis	
No	86 (89.6)
Yes	10 (10.4)
CRC differentiation	
Well/well to moderate	8 (11.8)
Moderate	57 (83.8)
Moderate to poor/poor	3 (4.4)
Smoking history	
No	68 (70.8)
Yes	28 (29.2)
RAS	
Wild type	10 (62.5)
mutant type	6 (37.5)
Bilateral pulmonary nodules	
No	91 (94.8)
Yes	5 (5.2)
LN sampling at PM	
No	51 (53.1)
Yes	45 (46.9)
Positive LN at PM	

No	90 (93.8)
Yes	6 (6.2)

CRC: Colorectal cancer; CEA: Carcinoembryonic antigen; LN: Lymph nodes; PM: Pulmonary metastases; RAS: Rat sarcoma; VATS: Video-assisted thoracoscopic surgery; DFI: Disease-free interval; IQR: Interquartile range.

In the entire cohort, 62 patients did not receive ACT, while 34 did. The groups did not show significant differences in sex, resection type, number of metastatic lesions, tumor size, bilateral pulmonary nodules, lymph node (LN) sampling during PM, or positive LN at PM when stratified by ACT. However, age at primary cancer diagnosis (P = 0.038), age at lung surgery (P = 0.014), and smoking history (P = 0.038) did differ (Table 2).

Table 2 Baseline characteristics and clinical outcomes of patients among groups before propensity analysis, *n* (%)

Factors	Levels	Surgery alone (*n* = 62)	Adjuvant chemotherapy (*n* = 34)	*P* value
Gender	Male	39 (62.9)	19 (55.9)	0.649
	Female	23 (37.1)	15 (44.1)	
Age at CRC diagnosis	mean ± SD	61.3 ± 9.9	56.9 ± 9.4	0.038
Age at time of pulmonary surgery	mean ± SD	64.4 ± 9.6	59.4 ± 9.0	0.014
Smoking history	No	39 (62.9)	29 (85.3)	0.038
	Yes	23 (37.1)	5 (14.7)	
Prior extra-thoracic metastasis	No	55 (88.7)	31 (91.2)	0.977
	Yes	7 (11.3)	3 (8.8)	
Access	Open	16 (25.8)	4 (11.8)	0.175
	VATS	46 (74.2)	30 (88.2)	
Type of resection	Lobe	30 (48.4)	12 (35.3)	0.307
	Segmental wedge	32 (51.6)	22 (64.7)	
Number of metastatic lesions	1	50 (80.6)	26 (76.5)	0.827
	> 1	12 (19.4)	8 (23.5)	
Tumor size (cm)	≤ 2cm	33 (53.2)	20 (58.8)	0.754
	> 2 cm	29 (46.8)	14 (41.2)	
Bilateral pulmonary nodules	No	59 (95.2)	32 (94.1)	1.000
	Yes	3 (4.8)	2 (5.9)	
LN sampling at PM	No	31 (50)	20 (58.8)	0.539
	Yes	31 (50)	14 (41.2)	
Positive LN at PM	No	59 (95.2)	31 (91.2)	0.741
	Yes	3 (4.8)	3 (8.8)	
CEA	≤ 5 ng/mL	40 (64.5)	21 (61.8)	0.963
	> 5 ng/mL	22 (35.5)	13 (38.2)	
DFI	mean ± SD	1070.1 ± 754.2	946.0 ± 620.6	0.415
Primary tumor location	Left colon	18 (29)	11 (32.4)	0.340
	Rectal	29 (46.8)	19 (55.9)	
	Right colon	15 (24.2)	4 (11.8)	

CRC: Colorectal cancer; CEA: Carcinoembryonic antigen; LN: Lymph nodes; PM: Pulmonary metastases; VATS: Video-assisted thoracoscopic surgery; DFI: Disease-free interval.

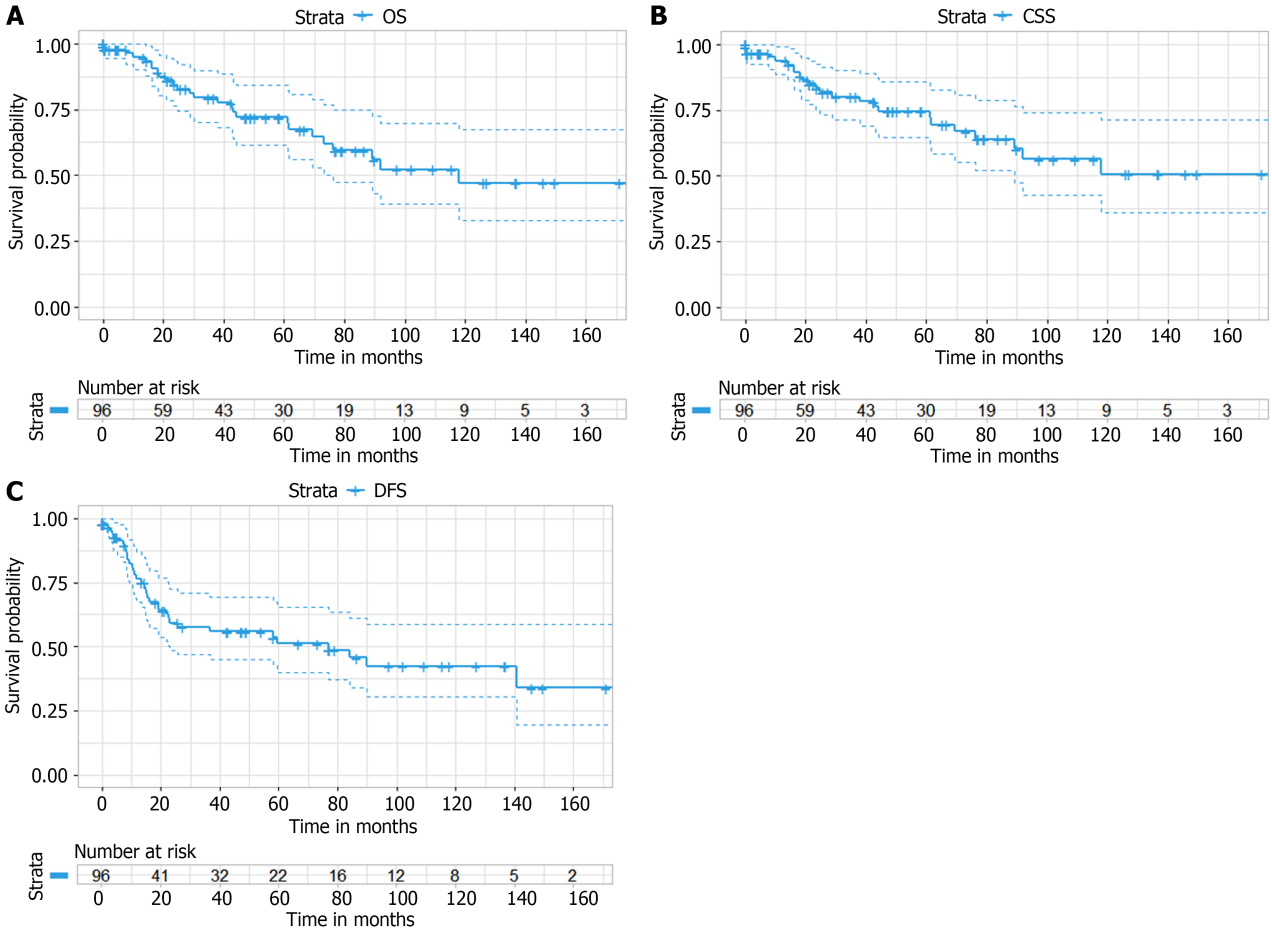

Figure 1 Kaplan-Meier method. A: Overall survival in all patients; B: Cancer-special survival in all patients; C: Disease-free survival in all patients. OS: Overall survival; CSS: Cancer-special survival; DFS: Disease-free survival.

Outcomes

The median follow-up was 27.5 months, with 26 patients having died by analysis. The OS rates at 1, 2, and 5 years were 94.8% [95% confidence interval (CI): 90.0%-99.9%], 99.9% (95%CI: 76.3%-93.4%), and 72.0% (95%CI: 61.6%-84.1%), respectively (Figure 1A). CSS rates at 1, 2, and 5 years were 93.7% (95%CI: 88.4%-99.2%), 83.4% (95%CI: 75.2%-92.5%), and 74.4% (95%CI: 64.5%-86.0%), respectively (Figure 1B). Progressive disease, defined as systemic and/or local progression or uncontrolled primary tumors, occurred in 36 patients (37.5%) at a median interval of 76.8 months. DFS rates at 1, 2, and 5 years were 76.4% (95%CI: 67.2%-87.0%), 57.6% (95%CI: 48.6%-72.3%) and 51.3% (95%CI: 40.1%-65.5%), respectively (Figure 1C).

After applying the IPTW method, the effective sample size was modestly altered, with data from 128 to 105 patients analyzed in the ACT after PM resection and PM resection alone groups. Kaplan-Meier analysis and the log-rank test showed no significant difference in time to death, the primary outcome, between the ACT after PM resection and PM resection alone groups, with OS favoring ACT after resection of PM (P = 0.08 before IPTW analysis; P = 0.15 after IPTW analysis) (Figure 2A-B). The P value of the stabilized IPTW analysis is 0.17. Meanwhile, after applying weights, the variables between the two groups maintained a substantial balance at the baseline level (Figure 3).

Table 3, Table 4, Table 5, and Table 6 summarize survival data according to risk factors before and after IPTW. CEA levels (P = 0.038) and prior extra-thoracic metastasis (P = 0.049) were significant predictors of survival. In multivariate analysis, prior extra-thoracic metastasis of PM [Hazard ratio (HR): 4.97; 95%CI: 1.03-24.08; P = 0.046] was associated with improved survival before and after IPTW, while the type of resection (HR: 0.45; 95%CI: 0.20-1.00; P = 0.049) and DFI (HR: 0.45; 95%CI: 0.20-0.98; P = 0.044) were confirmed as predictors OS in the original cohort.

Sensitivity analyses, encompassing data before and after imputation, complete case analysis, and propensity score-adjusted analysis, did not significantly change the results (Table 6 and Table 7; Figure 2C-E).

DISCUSSION

Although surgery for CRC metastasis to the lungs can improve patient prognosis, it remains far from ideal[23]. Current research is focused on improving outcomes for patients with CRC with lung metastases who undergo surgery[24]. Although patients with liver metastases from CRC can benefit from postoperative chemotherapy[25], it remains unclear whether patients with PM derive similar benefits from perioperative chemotherapy. The benefit of ACT for patients

Table 3 Univariable Cox proportional hazards model for overall survival after inverse probability of treatment-weighting

Factors		HR (univariable)
Gender	M	
	F	0.8556 (0.3201-2.287, *P* = 0.756)
Age at primary cancer	≤ 60 years	
	> 60 years	1.1914 (0.4402-3.224, *P* = 0.730)
Smoking history	No	
	Yes	1.07988 (0.3514-3.319, *P* = 0.893)
Age lung surgery	≤ 60 years	
	> 60 years	0.6498 (0.2495-1.692, *P* = 0.377)
Surgical approach for PM	Open	
	VATS	0.5052 (0.1863-1.37, *P* = 0.18)
Type of resection	Lobectomy	
	Sublobar resection	0.6032 (0.2248-1.619, *P* = 0.065)
Lymph node dissection	No	
	Yes	1.2383 (0.4682-2.728, *P* = 0.667)
Positive LN at PM	No	
	Yes	0.9268 (0.1181-7.271, *P* = 0.942)
Adjuvant chemotherapy	No	
	Yes	0.4204 (0.1632-1.083, *P* = 0.0726)
Primary tumor location	Left colon	
	Right colon	0.4590 (0.1093-1.928, *P* = 0.288)
	Rectum	0.6267 (0.2328-1.687, *P* = 0.355)
CEA levels	≤ 5 ng/mL	
	> 5 ng/mL	2.7261 (1.075-6.913, *P* = 0.0347)
Number of metastatic lesions	1	
	> 1	2.1928 (0.8496-5.66, *P* = 0.105)
Bilateral pulmonary nodules	No	
	Yes	2.478 (0.9703-6.329, *P* = 0.0578)
Tumor size (cm)	≤ 2 cm	
	> 2 cm	0.7971 (0.2961-2.146, *P* = 0.653)
Prior extra-thoracic metastasis	No	
	Yes	4.627 (1.01-21.2, *P* = 0.0485)

CRC: Colorectal cancer; CEA: Carcinoembryonic antigen; PM: Pulmonary metastases; VATS: Video-assisted thoracoscopic surgery; HR: Hazard ratio; M: Male; F: Female.

Table 4 Multivariate analysis of overall survival after inverse probability of treatment-weighting

Survival		HR	95%CI	*P* value
Adjuvant chemotherapy	No			
	Yes	0.43	0.16-1.18	0.10
Number of metastatic lesions	1			
	≥ 2	1.95	0.64-5.93	0.24

Prior extra-thoracic metastasis	No			
	Yes	4.97	1.03-24.08	0.046
Bilateral pulmonary nodules	No			
	Yes	1.84	0.36-9.43	0.47
CEA	≤ 5 ng/mL			
	> 5 ng/mL	2.00	0.76-5.28	0.16
Type of resection	Lobectomy			
	Sublobar resection	0.53	0.21-1.35	0.19

HR: Hazard ratio; CEA: Carcinoembryonic antigen; CI: Confidence interval.

Table 5 Univariable Cox proportional hazards model for overall survival in the original cohort

Factors		HR (univariable)
Gender	M	
	F	0.78 (0.35-1.77, *P* = 0.555)
Age at primary cancer	≤ 60 years	
	> 60 years	1.41 (0.65-3.05, *P* = 0.381)
Smoking history	No	
	Yes	1.11 (0.48-2.55, *P* = 0.814)
Age lung surgery	≤ 60 years	
	> 60 years	0.98 (0.45-2.12, *P* = 0.956)
Surgical approach for PM	Open	
	VATS	0.77 (0.32-1.84, *P* = 0.556)
Type of resection	Lobectomy	
	Sublobar resection	0.47 (0.21-1.04, *P* = 0.062)
Lymph node dissection	No	
	Yes	1.18 (0.55-2.55, *P* = 0.674)
Positive LN at PM	No	
	Yes	0.62 (0.08-4.60, *P* = 0.642)
Adjuvant chemotherapy	No	
	Yes	0.47 (0.20-1.12, *P* = 0.087)
Primary tumor location	Left colon	
	Right colon	0.91 (0.32-2.63, *P* = 0.863)
	Rectum	0.60 (0.24-1.53, *P* = 0.288)
CEA levels	≤ 5 ng/mL	
	> 5 ng/mL	1.48 (0.66-3.31, *P* = 0.335)
Number of metastatic lesions	1	
	> 1	1.75 (0.73-4.23, *P* = 0.211)
Bilateral pulmonary nodules	No	
	Yes	1.88 (0.44-8.08, *P* = 0.398)
Tumor size (cm)	≤ 2 cm	
	> 2 cm	0.67 (0.29-1.53, *P* = 0.337)
Prior extra-thoracic metastasis	No	

	Yes	1.94 (0.58-6.50, *P* = 0.283)
DFI	≤ 600	
	> 600	0.48 (0.22-1.04, *P* = 0.063)

CEA: Carcinoembryonic antigen; HR: Hazard ratio; M: Male; F: Female; LN: Lymph nodes; PM: Pulmonary metastases; VATS: Video-assisted thoracoscopic surgery; DFI: Disease-free interval.

Table 6 Multivariate analysis of overall survival in the original cohort

Survival		HR	95%CI	*P* value
Adjuvant chemotherapy	No			
	Yes	0.50	0.21-1.18	0.114
Type of resection	Lobectomy			
	Sublobar resection	0.45	0.20-1.00	0.049
DFI	≤ 600			
	> 600	0.45	0.20-0.98	0.044

HR: Hazard ratio; CI: Confidence interval; DFI: Disease-free interval.

Table 7 Clinical, radiological, and histological characteristics of the population: Pre-imputation and post-imputation, *n* (%)

Factors	Levels	Post-imputation (*n* = 96)	Pre-imputation (*n* = 96)	*P* value
Gender	Male	58 (60.4)	58 (60.4)	1.000
	Female	38 (39.6)	38 (39.6)	
Age at CRC diagnosis	mean ± SD	59.7 ± 9.9	59.7 ± 9.9	1.000
Age at time of pulmonary surgery	mean ± SD	62.6 ± 9.6	62.6 ± 9.6	1.000
Smoking history	No	68 (70.8)	68 (70.8)	1.000
	Yes	28 (29.2)	28 (29.2)	
Adjuvant chemotherapy for CRC	No	30 (31.2)	30 (31.2)	1.000
	Yes	66 (68.8)	66 (68.8)	
CRC differentiation	Moderate	84 (87.5)	57 (83.8)	0.760
	Moderate to poor	4 (4.2)	3 (4.4)	
	Well to moderate	8 (8.3)	8 (11.8)	
Primary tumor T stage	T1 or T2	10 (10.4)	8 (11.8)	0.985
	T3 or T4	86 (89.6)	60 (88.2)	
Primary tumor N stage	N0	39 (40.6)	28 (39.4)	1.000
	N1 or N2	57 (59.4)	43 (60.6)	
Prior extra-thoracic metastasis	No	86 (89.6)	86 (89.6)	1.000
	Yes	10 (10.4)	10 (10.4)	
Access	Open	20 (20.8)	20 (20.8)	1.000
	VATS	76 (79.2)	76 (79.2)	
Type of resection	Lobe	42 (43.8)	42 (43.8)	1.000
	Segmental wedge	54 (56.2)	54 (56.2)	
Number of metastatic lesions	1	76 (79.2)	76 (79.2)	1.000
	> 1	20 (20.8)	20 (20.8)	

Tumor size (cm)	≤ 2	53 (55.2)	51 (54.8)	1.000
	> 2	43 (44.8)	42 (45.2)	
Bilateral pulmonary nodules	No	91 (94.8)	91 (94.8)	1.000
	Yes	5 (5.2)	5 (5.2)	
LN sampling at PM	No	51 (53.1)	51 (53.1)	1.000
	Yes	45 (46.9)	45 (46.9)	
Positive LN at PM	No	90 (93.8)	90 (93.8)	1.000
	Yes	6 (6.2)	6 (6.2)	
CEA levels	≤ 5 ng/mL	61 (63.5)	47 (60.3)	0.774
	> 5 ng/mL	35 (36.5)	31 (39.7)	
CRC LVI	No	81 (84.4)	45 (81.8)	0.858
	Yes	15 (15.6)	10 (18.2)	
CRC PNI	No	77 (80.2)	41 (74.5)	0.545
	Yes	19 (19.8)	14 (25.5)	
Adjuvant chemotherapy	No	62 (64.6)	62 (64.6)	1.000
	Yes	34 (35.4)	34 (35.4)	
DFI	mean ± SD	1026.2 ± 708.9	1026.2 ± 708.9	1.000
Primary tumor location	Left colon	29 (30.2)	29 (33)	0.921
	Rectal	48 (50)	42 (47.7)	
	Right colon	19 (19.8)	17 (19.3)	

CRC: Colorectal cancer; CEA: Carcinoembryonic antigen; LN: Lymph nodes; PM: Pulmonary metastases; VATS: Video-assisted thoracoscopic surgery; DFI: Disease-free interval; LVI: Lymphovascular invasion; PNI: Perineural invasion.

achieving no evidence of disease (NED) after PM resection is still debated. For example, a meta-analysis by Zhang *et al* [18] found no improvement in prognosis with postoperative ACT for CRC lung metastasis, whereas a meta-analysis by Li and Qin[17] suggested that perioperative chemotherapy could enhance outcomes. These two meta-analyses, which investigated the impact of chemotherapy on the prognosis of patients undergoing resection of CRC lung metastases, reached different conclusions. As a result, it remains unclear whether the mode of chemotherapy-whether neoadjuvant, adjuvant, or both-affects the prognosis of these patients. Supporting this uncertainty, Pagès *et al*[26] found that neoadjuvant chemotherapy did not significantly improve patient prognosis.

In this study, we retrospectively analyzed the need for ACT in patients who underwent lung metastasectomy for CRC at our center. The HR estimation indicated that patients did not benefit from ACT after lung metastasis resection (HR: 0.50; 95%CI: 0.21-1.18; $P = 0.114$). Multivariate analysis adjusting for other survival-influencing variables confirmed that postoperative ACT did not significantly alter OS, CSS, or DFS, consistent with previous meta-studies[18].

The role of a history of liver metastasis as a prognostic factor in patients undergoing pulmonary metastasectomy has been controversial[27]. Although some studies dismiss liver metastasis history as a significant survival factor, others have reached the opposite conclusion[23]. Indeed we identified it as an independent adverse prognostic factor for OS ($P = 0.046$) after inverse probability of treatment-weighting. Additionally, preoperative CEA levels were significantly associated with OS, aligning with many studies that report high CEA levels (greater than 5 ng/mL) as a negative prognostic factor in CRC patients undergoing pulmonary metastasectomy[27,28].

The DFI between CRC resection and the development of lung metastasis has consistently been shown to correlate with treatment outcomes, though studies vary in defining the cutoff for a prolonged DFI[29-32]. A pooled analysis indicated that a DFI of less than 36 months is a poor prognostic factor for OS[29]. In this study, the optimal DFI cutoff, calculated using the Youden index, was 20 months, with shorter DFI's predicting worse outcomes. Interestingly, while previous studies have identified the number of lung metastases as a key adverse prognostic factor, our study did not find a significant correlation, likely due to the exclusion of patients with more than five lung metastases, unlike prior studies that included patients with over 10 metastases[33,34].

There is ongoing debate about whether open thoracic surgery offers superior outcomes compared to video-assisted thoracic surgery (VATS) for CRC lung metastasis. Open surgery allows for the palpation of the lungs to identify occult metastases not visible on imaging, traditionally making it the gold standard[35]. However, recent studies, including a multi-institutional retrospective analysis from Japan, found no significant difference in survival rates between open surgery and VATS after propensity score adjustment[36]. Similarly, our study found comparable survival outcomes between patients undergoing VATS and those undergoing open surgery.

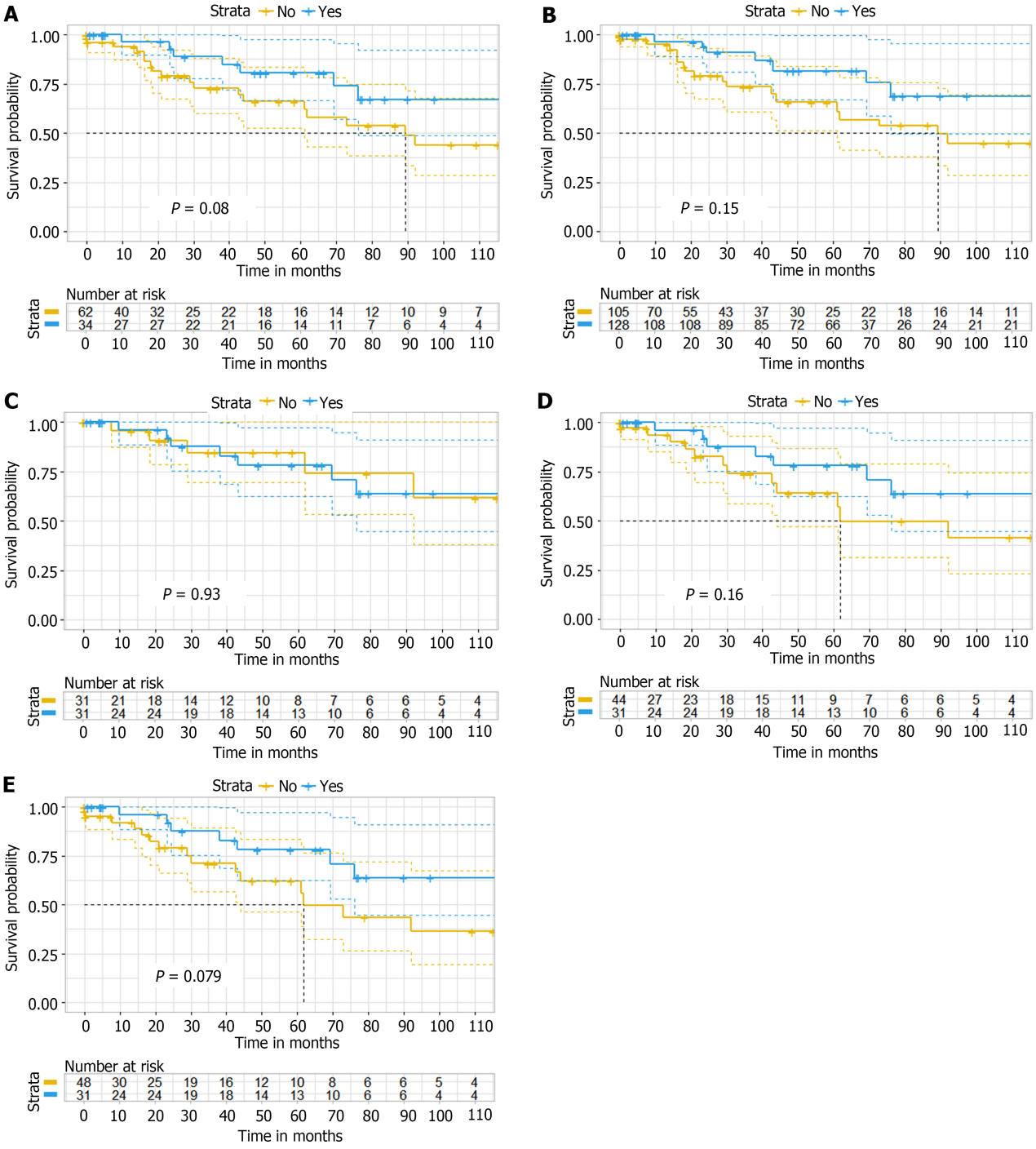

Figure 2 Kaplan-Meier survival curves according to adjuvant chemotherapy with lung metastases. A: In the original cohort; B: After inverse probability of treatment-weighting analysis; C: After propensity score-matching analysis (ratio = 1); D: After propensity score-matching analysis (ratio = 2); E: After propensity score-matching analysis (ratio = 3).

This study had several limitations. First, it is a retrospective, single-center study which may introduce selection bias. Second, the diverse chemotherapy regimens, doses, and cycles may have influenced the conclusions. The study only included carefully selected patients excluding many with CRC lung metastases. Furthermore, the decision to administer ACT was influenced by clinical decision-making factors specific to a single institution, potentially causing imbalances. Notably patients who received postoperative ACT were younger at CRC diagnosis, had earlier lung metastases, and shorter median DFI than those who did not receive ACT. These patients might have had more aggressive tumors but also better to responses to cytotoxic therapy. These factors must be considered when interpreting the study's results.

CONCLUSION

In conclusion, our findings indicate that ACT does not confer survival benefits for patients who reach NED after PM

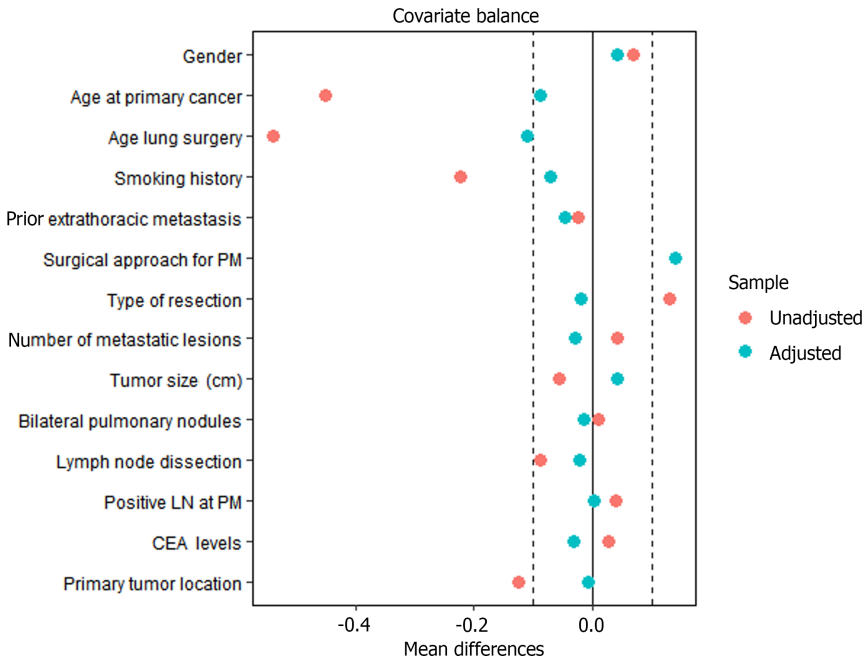

Figure 3 Standardized mean difference before and after inverse probability of treatment-weighting. CEA: Carcinoembryonic antigen; LN: Lymph nodes; PM: Pulmonary metastases.

resection. However, this conclusion is limited by the retrospective nature of the analysis, underscoring the need for randomized controlled trials focused on ACT in this specific patient subgroup.

FOOTNOTES

Author contributions: Gao Z and Jin X prepared the manuscript; Wu SK, Wang X and Jin X conceived the review, and edited the manuscript; Gao Z collected and analyzed the data; Zhang SJ and Wu YC analyzed the data and drafted the manuscript; All the authors have read and approved the final version of the manuscript.

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