International Journal of Colorectal Disease (2025) 40:191
https://doi.org/10.1007/s00384-025-04986-8

RESEARCH

Neoadjuvant therapy for resectable colorectal cancer pulmonary oligometastases: a retrospective cohort study

Yibo Cai[1] · Guohui Xu[2] · Yanxi Shao[1,3] · Dening Ma[1] · Yuping Zhu[1]

Received: 10 April 2025 / Accepted: 14 August 2025

Abstract

Purpose Lung metastasectomy has been considered the cornerstone of treatment of resectable colorectal cancer pulmonary oligometastases (CRCPOM). However, the role of chemotherapy in the neoadjuvant setting remains unclear. This study aimed to determine whether neoadjuvant therapy (NAT) could further improve survival outcomes of patients with resectable CRCPOM.

Methods We included all 253 consecutive patients at our center between 2010 and 2022. Propensity score matching (PSM) was performed to balance the baseline characteristics. The efficacy of NAT was evaluated using the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1). Disease-free survival (DFS) was the primary endpoint, which was estimated by the Kaplan–Meier method. Multivariate analyses were conducted using Cox proportional hazards regression to identify independent predictors.

Results The cumulative 5- and 10-year DFS rates following lung metastasectomy were 48.3% and 39.4%, respectively. After PSM, NAT was significantly associated with improved DFS (HR, 0.52; $P = 0.009$). A clinical risk score was constructed using four independent predictors of worse DFS (serum carcinoembryonic antigen > 5.0 ng/mL, disease-free interval after colorectal resection < 2 years, primary tumor with nodal involvement, extrapulmonary metastases) and enabled risk stratification. The administration of NAT could improve DFS in patients with ≥ 1 risk factor (HR, 0.60; $P = 0.020$), while such benefit was not observed in those with no risk factor. RECIST-defined response was noted in 34/74 (46.0%) patients who received NAT, which was correlated with improvement in DFS (HR, 0.31; $P = 0.008$).

Conclusions NAT may confer a survival benefit in patients with resectable CRCPOM. Using an easy-to-use clinical risk score, patients with ≥ 1 risk factor are good candidates for initial NAT. The RECIST criteria are deemed suitable for the assessment of efficacy of NAT before lung metastasectomy.

Keywords Colorectal cancer pulmonary oligometastases · Neoadjuvant therapy · Lung metastasectomy · Clinical risk score · Disease-free survival

Introduction

Colorectal cancer (CRC) is one of the most common fatal malignancies with a high risk of metastasis and recurrence worldwide; additionally, approximately half of patients develop metastases at some point during the course of the disease [1, 2]. The lung is the second most common site of CRC metastasis after the liver, accounting for 29.0–32.9% of all metastatic cases [3, 4]. In 1995, Hellman and Weichselbaum first proposed the concept of oligometastasis, which was described as an intermediate state occurring between localized disease and widespread metastasis [5]. According to the current ESMO guidelines, a consensus definition of oligometastatic CRC for clinically "actionable" patients is as

Yibo Cai and Guohui Xu contributed equally to this work.

✉ Dening Ma
madeningsdu@163.com

✉ Yuping Zhu
drzyp@163.com

[1] Department of Colorectal Surgery, Zhejiang Cancer Hospital, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, Hangzhou, Zhejiang, China

[2] Department of Gastrointestinal Surgery, Tongxiang Second People's Hospital, Tongxiang, Zhejiang, China

[3] Postgraduate Training Base Alliance of Wenzhou Medical University, Hangzhou, Zhejiang, China

Published online: 29 August 2025

follows: "One to five metastatic lesions; up to two metastatic sites; controlled primary tumor (optionally resected); and all metastatic sites must be safely treatable by local treatments" [6]. Thus, considering the restricted tumor metastatic capacity, aggressive surgical resection has been the mainstay of treatment in patients with colorectal cancer pulmonary oligometastases (CRCPOM) [3]. Previous studies have reported that a 5-year overall survival (OS) rate of 24–68% can be achieved if resectable CRCPOM patients undergo lung metastasectomy, with this rate being significantly greater than that of patients who receive chemotherapy alone [3, 7–11].

Moreover, the additional role of perioperative (neoadjuvant and adjuvant) chemotherapy in the setting of resected CRCPOM is gradually being explored. Unexpectedly, numerous studies have demonstrated that adjuvant chemotherapy does not improve long-term outcomes for patients with resectable CRCPOM [12–14]. Neoadjuvant chemotherapy has recently been suggested to facilitate resectability, eliminate micrometastasis, and reduce the risk of relapse after hepatectomy [15]. Thus, this preoperative therapeutic strategy has been established as an important treatment option and recommended by the NCCN and ESMO guidelines for patients with resectable colorectal liver metastases exhibiting a high risk of recurrence [16, 17]. However, to our knowledge, few studies have specifically addressed the role of neoadjuvant chemotherapy in resectable CRCPOM, and the clinical benefit of neoadjuvant therapy (NAT) remains uncertain. Although some experts argue that preoperative systemic therapy can aid in assessing tumor biological behavior, there is an absence of high-quality clinical data or definitive evidence regarding this potential application and consequently no clear recommendation of neoadjuvant chemotherapy in CRCPOM [3].

Therefore, we performed a retrospective cohort study to explore the efficacy of neoadjuvant chemotherapy with or without targeted agents. An additional secondary objective of the study was to identify the predictors for recurrence after lung metastasectomy and subsequently construct an easy-to-use clinical risk score for postoperative recurrence to guide appropriate NAT in patients with resectable CRCPOM.

Materials and methods

Study cohort

This retrospective study cohort included all consecutive patients who underwent lung metastasectomy of resectable pulmonary oligometastases from colorectal cancer in the Zhejiang Cancer Hospital between January 2010 and December 2022. Patients with any of the following were excluded: more than five metastatic lesions; more than one extrapulmonary metastatic organ; the primary tumor, pulmonary or extrapulmonary metastases were unresectable at the time of initial diagnosis; or receiving ablative techniques (radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation) or SBRT for local treatment of lung oligometastases.

Perioperative management and surgical approach

The resectability of lung metastases was defined as the complete removal of all macroscopic metastases and the achievement of negative margins (≥ 2 cm of normal tissue around the metastatic lesions). The assessment of resectability was evaluated by a multidisciplinary team (MDT) consisting of radiologists, surgeons, and oncologists, and the specific criteria are described in the eAppendix in the Supplement. Upfront lung metastasectomy or NAT was initiated if patients were diagnosed with resectable CRCPOM. The selection of neoadjuvant therapy was determined according to the metastatic burden, the MDT decision, and patient choice. Patients with synchronous, multiple, or bilateral lung metastases; elevated CEA levels; extrapulmonary metastases; or specific genetic mutations (e.g., RAS/RAF status) were considered to be suitable for neoadjuvant therapy. At least two cycles of 5-FU-based chemotherapy with or without targeted agents were administered to these patients. All of the patients receiving NAT underwent baseline and preoperative chest computed tomography (CT) scans. The response to NAT was evaluated using the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) [18]. Surgical procedures for lung metastasectomy included wedge resection, segmentectomy, or lobectomy. No patients in the present study underwent pneumonectomy. For patients with bilateral metastases, staged resection was permissible. Selective ipsilateral hilar and mediastinal lymph node dissections were simultaneously performed in patients with clinically positive nodal metastases. When extrapulmonary oligometastases (such as liver metastases) were synchronously detected, resection or ablation was recommended to achieve no evidence of disease (NED) status. Postoperative follow-up examinations were regularly performed according to NCCN guidelines [16]. Referring to the current guidelines for colorectal liver metastases, adjuvant FU-based chemotherapy was typically recommended for all patients after lung metastasectomy with the aim of decreasing the risk of recurrence and metastasis. However, more than half of the patients (61.7%) in our cohort refused adjuvant chemotherapy.

Variables and definitions

According to the literature, demographic, primary tumor-related, pulmonary metastasis-related, and treatment

information was retrospectively collected in the present study. The serum carcinoembryonic antigen (CEA) level was measured before lung metastasectomy, and CEA concentrations ≤ 5 ng/mL were considered to be within the reference range. For the status of the resection margins of pulmonary metastases, R0 resection was defined as no residual tumor status with a microscopically negative margin, whereas R1 resection indicated microscopically positive margins, and R2 resection indicated the presence of any gross residual tumors. The disease-free interval (DFI) was defined as the time interval ranging from primary tumor resection to the detection of pulmonary oligometastases. Given the influence of adjuvant chemotherapy after surgical resection of the primary tumor on our outcomes, we excluded all patients that have a DFI ≤ 6 before diagnosis of resectable CRCPOM. We defined synchronous metastases if the time period between the diagnosis of primary tumor and the detection of pulmonary oligometastases was within 6 months; moreover, metachronous metastases were defined if the time period was later than 6 months. Our primary endpoint was disease-free survival (DFS), which was calculated from the date of lung metastasectomy to the date of relapse, death, or the last follow-up visit. Overall survival (OS) was also assessed as a secondary endpoint and was defined as the time interval from lung metastasectomy to death from any cause or the last follow-up visit.

Statistical analysis

Continuous variables were summarized as the median and interquartile range (IQR), and categorical variables were summarized as counts and percentages. Statistical significance was evaluated by the Student's *t* test, chi-square test, or Fisher's exact test. Propensity score matching (PSM) was performed using a 2:1 nearest neighbor algorithm with a caliper width of 0.1 to control selection bias. The DFS and OS curves were estimated by the Kaplan–Meier method and compared with the log-rank test. The multivariate Cox proportional hazards regression models were used to determine hazard ratios (HR) and confidence intervals (CI). All statistical analyses were performed by SPSS 23.0 (SPSS Inc., IBM Corporation, Chicago, IL). A two-sided P value < 0.05 indicated statistical significance.

Results

Clinicopathological and treatment characteristics

A total of 253 individuals were enrolled in the present study, of whom 74 initially received NAT (NAT group, 29.2%), and 179 received upfront lung metastasectomy alone (without NAT group, 70.8%). The demographic, clinicopathological, and treatment characteristics of patients with CRCPOM are summarized in Table 1. Most of the patients were male and never smokers, and the median age at baseline was 60 years (IQR 54–66 years). Preoperative CEA levels were elevated in 28.9% of the patients. The majority of the patients (60.8%) exhibited a DFI from colorectal resection to detection of metastatic disease of < 2 years, and 21 patients (8.3%) had a history of extrapulmonary metastases. The median maximum size of the pulmonary metastases was 15 mm (IQR 10–25 mm). Solitary pulmonary metastasis was present in 71.9% of the patients, and synchronous and bilateral pulmonary metastases were observed in 21.3% and 20.0%, respectively. Wedge resection or segmentectomy ($n = 160$, 63.2%) and lobectomy ($n = 93$, 26.8%) were performed via thoracotomy or thoracoscopy. No patients underwent R1/R2 resection with positive surgical margins. Among 105 patients who received additional lymphadenectomy, only 10.5% (11 patients) presented with histologically positive lymph nodes. Moreover, RAS (KRAS or NRAS) or BRAF mutations were identified in 58 (69.9%) of 83 patients, which were more commonly detected in the NAT group. Adjuvant chemotherapy was only administered in 38.3% of the patients and was more likely to be used in those who had received prior NAT (48.6% versus 34.1%; $P = 0.030$). Patients with elevated CEA levels (35.1% versus 22.9%; $P = 0.045$), multiple metastases (41.9% versus 22.3%; $P = 0.002$), synchronous metastases (31.1% versus 17.3%; $P = 0.015$), bilateral pulmonary metastases (31.1% versus 14.0%; $P = 0.002$), and pleural invasion (23.0% versus 12.3%; $P = 0.032$) were more likely to receive NAT. After a 2:1 ratio PSM, 110 patients in the without NAT group and 54 patients in the NAT group were retained for comparison, and all characteristics were balanced between the two groups (Table S1).

Survival outcome

After a median follow-up duration of 71.0 months (95% CI, 64.7–77.3), the cumulative 3-year, 5-year, and 10-year DFS rates for all patients were 54.9%, 48.3%, and 39.4%, while the corresponding OS rates were 88.0%, 70.6%, and 46.2%, respectively. In the multivariable analysis, NAT appeared to be significantly associated with improved DFS (HR, 0.49; 95% CI, 0.32–0.74; $P = 0.001$) and OS (HR, 0.51; 95% CI, 0.29–0.88; $P = 0.015$) compared with upfront lung metastasectomy (Fig. 1A, 1 and Table 2). Furthermore, this substantial survival benefit of NAT for DFS (HR, 0.52; 95% CI, 0.32–0.85; $P = 0.009$) remained significant after PSM (Fig. 1C). Notably, as shown in Figure S1 and Table S2, adjuvant chemotherapy did not provide an apparent survival benefit in patients with CRCPOM (DFS: HR, 1.41; 95% CI, 0.94–2.12; $P = 0.096$;

Table 1 Clinicopathological characteristics andtreatment information of patients with resectable CRCPOM

Variable	Without NAT (%)	With NAT (%)	*P*-value[a]
Total patients	179 (70.8%)	74 (29.2%)	
Age (years) (median; IQR)	60 (54–66)	61 (54–66)	0.770
Gender			0.925
Male	115 (70.6%)	48 (71.1%)	
Female	64 (29.4%)	26 (28.9%)	
Smoking			0.621
Yes	69 (38.5%)	31 (41.9%)	
No	110 (61.5%)	43 (58.1%)	
Primary tumor			
Location			0.018
Right-sided colon	42 (23.5%)	7 (9.5%)	
Left-sided colon	30 (16.8%)	10 (13.5%)	
Rectum	109 (59.8%)	57 (77.0%)	
Histological type			0.727
Adenocarcinoma	162 (90.5%)	68 (91.9%)	
Mucinous adenocarcinoma	17 (9.5%)	6 (8.1%)	
T stage			0.134
$T_{1–3}$	96 (53.6%)	30 (40.5%)	
T_4	66 (36.9%)	37 (50.0%)	
Unknown	17 (9.5%)	7 (9.5%)	
N stage			0.728
N_0	75 (41.9%)	32 (43.2%)	
N_1	66 (36.9%)	24 (32.4%)	
N_2	23 (12.8%)	13 (17.6%)	
Unknown	15 (8.4%)	5 (6.8%)	
MMR status			0.019[b]
dMMR	4 (2.2%)	0 (0.0%)	
pMMR	104 (58.1%)	55 (74.3%)	
Unknown	71 (39.7%)	19 (25.7%)	
Lung metastasis			
Preoperative serum CEA (ng/mL)			0.045
≤ 5.0	138 (77.1%)	48 (64.9%)	
> 5.0	41 (22.9%)	26 (35.1%)	
Preoperative PET-CT			0.320
Yes	47 (26.3%)	24 (32.4%)	
No	132 (73.7%)	50 (67.6%)	
Number of lung metastases			0.002
Solitary	139 (77.7%)	43 (58.1%)	
Multiple	40 (22.3%)	31 (41.9%)	
Preoperative tumor size (mm) (median; IQR) 14 (10–23)		17 (11–25)	0.434
Pattern of lung metastasis			0.015
Synchronous	31 (17.3%)	23 (31.1%)	
Metachronous	148 (82.7%)	51 (68.9%)	
Tumor distribution			
Unilateral	154 (86.0%)	51 (68.9%)	0.002
Bilateral	25 (14.0%)	23 (31.1%)	
Extrapulmonary metastasis			0.352
Yes	13 (7.3%)	8 (10.8%)	
No	166 (92.7%)	66 (89.2%)	
KRAS/NRAS/BRAF mutation			< 0.001

Table 1 (continued)

Variable	Without NAT (%)	With NAT (%)	*P*-value[a]
KRAS/NRAS mut	29 (16.2%)	28 (37.8%)	
BRAF mut	0 (0.0%)	1 (1.4%)	
Wild	17 (9.5%)	8 (10.8%)	
Unknown	133 (74.3%)	37 (50.0%)	
DFI after colorectal resection (months)			0.550
< 24	106 (59.2%)	48 (64.9%)	
≥ 24	73 (40.8%)	26 (35.1%)	
Therapy			
Response to preoperative chemotherapy (RECIST 1.1)			NA
CR/PR		34 (45.9%)	
SD/PD		40 (54.1%)	
Operative procedure			0.954
Wedge resection/segmentectomy	113 (63.1%)	47 (63.5)	
Lobectomy	66 (36.9%)	27 (36.5)	
Pleural invasion			0.029
Positive	22 (12.3%)	17 (23.3)	
Negative	157 (87.7%)	56 (76.7)	
Vascular invasion (lung metastasis)			0.856
Positive	11 (6.1%)	5 (6.8%)	
Negative	168 (93.9%)	69 (93.2%)	
Resection status (lung metastasis)			NA
R0	179 (100.0%)	74 (100.0%)	
R1-2	0 (0.0%)	0 (0.0%)	
Thoracic lymph node involvement			0.773[b]
N-	64 (35.8%)	30 (40.5%)	
N+	8 (4.5%)	3 (4.1%)	
Without lymph node dissection	107 (59.8%)	41 (55.4%)	
Adjuvant chemotherapy			0.030
Yes	61 (34.1%)	36 (48.6%)	
No	118 (65.9%)	38 (51.4%)	

CRCPOM colorectal cancer pulmonary oligometastases, *NAT* neoadjuvant therapy, *IQR* interquartile range, *MMR* mismatch repair, *CEA* carcinoembryonic antigen, *DFI* disease-free interval, *RECIST* Response Evaluation Criteria in Solid Tumors, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NA* not applicable

[a]Pearson chi-square test or Student's *t* test

[b]Fisher's exact test

OS: HR, 0.72; 95% CI, 0.42–1.22; $P = 0.220$). Subgroup analyses according to whether NAT was administrated also demonstrated that adjuvant chemotherapy was not associated with improved survival outcomes (Figure S2). After adjustments for potential confounding factors, serum CEA > 5.0 ng/mL before lung metastasectomy (HR, 1.84, $P = 0.002$), extrapulmonary metastases (HR, 2.26, $P = 0.010$), DFI < 2 years after CRC resection (HR, 1.89, $P = 0.001$), and primary tumors with lymph node involvement (HR, 1.68, $P = 0.009$) were observed to be independent predictors for inferior DFS in patients with CRCPOM (Table 2).

Subgroup survival analysis of NAT in the different risk groups

According to the four previously identified prognostic factors (including serum CEA > 5.0 ng/mL before lung metastasectomy, extrapulmonary metastases, DFI < 2 years after CRC resection, and lymph node involvement of the primary tumor), patients with CRCPOM were divided into three recurrence-risk categories (low, 0 risk factors; moderate, 1–2 risk factors; and high, 3–4 risk factors) at initial diagnosis. The 5-year DFS rates of patients in the low-, moderate-, and high-risk groups were 79.5%, 48.8%, and 24.2%, respectively. Patients assigned to the

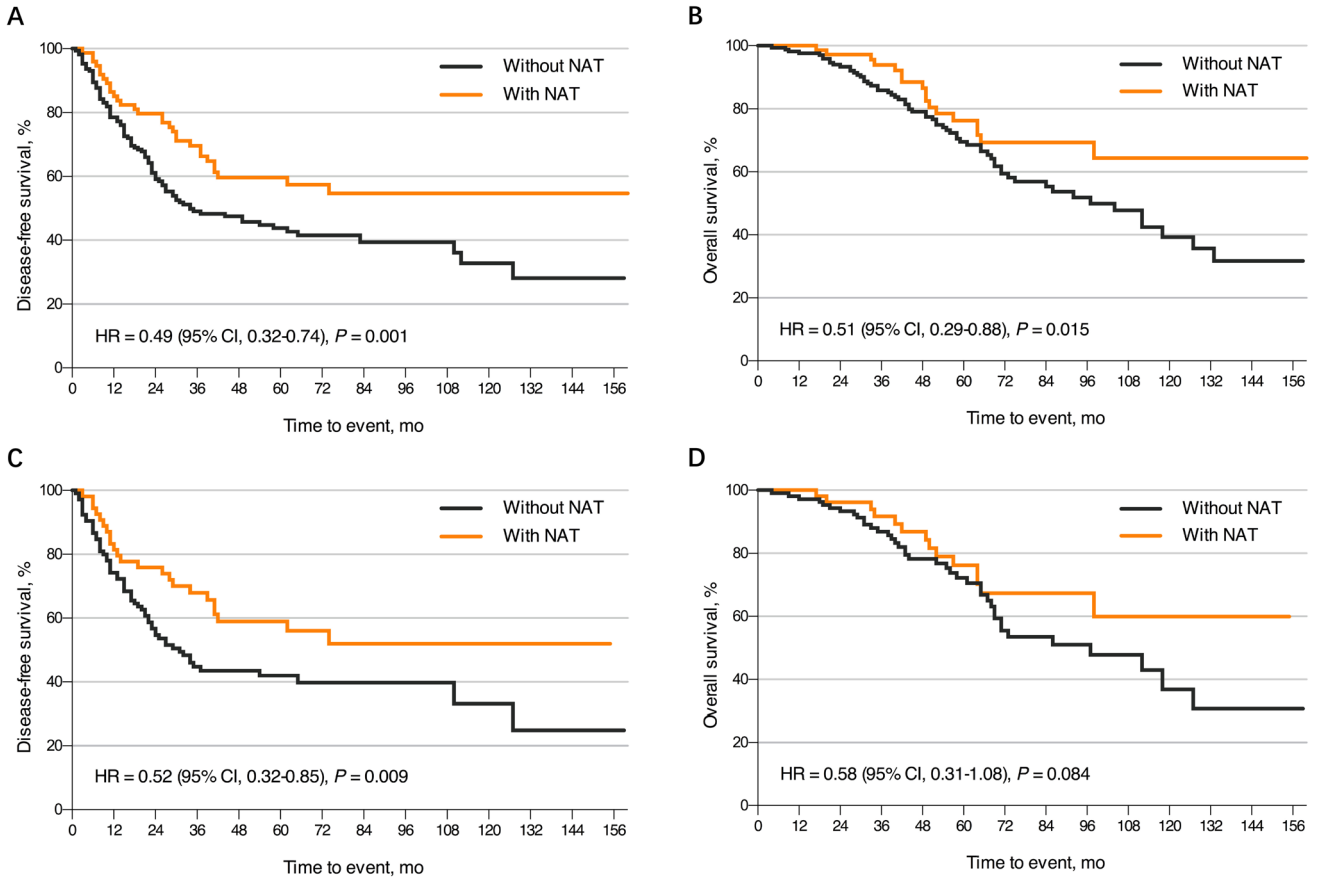

Fig. 1 Kaplan–Meier survival curves for CRCPOM patients treated with or without NAT. **A** DFS before PSM. **B** OS before PSM. **C** DFS after PSM. **D** OS after PSM. Abbreviations: *CRCPOM* colorectal cancer pulmonary oligometastases, *NAT* neoadjuvant therapy, *DFS* disease-free survival, *PSM* propensity score matching, *OS* overall survival

high-risk group (HR, 8.51; 95% CI, 2.89–25.03; $P < 0.001$) or moderate-risk group (HR, 3.80; 95% CI, 1.39–10.37; $P = 0.009$) had significantly worse DFS than patients in the low-risk group (Fig. 2A). In the high- and moderate-risk groups, 44.4% and 28.5% of the patients received NAT. Compared with lung metastasectomy alone, NAT significantly prolonged DFS (HR, 0.60; 95% CI, 0.39–0.92; $P = 0.020$) (Fig. 2C). Conversely, in the low-risk group, 27.3% of the patients received NAT, and an improvement in DFS was no longer observed in patients with NAT (HR, 0.77; 95% CI, 0.08–7.49; $P = 0.825$) (Fig. 2B).

Response evaluation of NAT

According to the RECIST 1.1 criteria, one patient (1.4%) had a complete response (CR), 33 patients (44.6%) had a partial response (PR), 33 patients (37.8%) had stable disease (SD), and 12 patients (16.2%) had progressive disease (PD). The 5-year DFS rate was 76.9% for responders (CR/PR) versus 45.1% for non-responders (SD/PD) ($P = 0.004$; HR, 0.31; 95% CI, 0.13–0.74; $P = 0.008$) (Table 3 and Fig. 3). After progression or discontinuation of first-line NAT, second-line NAT was administered to 10 of 74 patients (13.5%). Half of the patients received > 4 cycles of NAT, and 27.0% of the patients were simultaneously treated with a targeted agent. Notably, we observed that the significant difference in DFS among the three relapse risk groups became less apparent after the administration of NAT (both $P > 0.05$) (Table 3).

Discussion

In the present study, the 3-year and 5-year DFS rates of patients with resectable CRCPOM who underwent lung metastasectomy with or without NAT for pulmonary oligometastases were 54.9% and 48.3%, respectively, which were better than those reported in previous retrospective studies that included eligible patients before 2008 [19, 20]. This shift in the DFS rates may be due to advances in cancer therapies, such as minimally invasive surgical techniques, routine MDT practices, and the formulation

Table 2 Multivariate analysis of prognostic factors associated with disease-free and overall survival

Variable	DFS			OS		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Preoperative serum CEA (ng/mL)						
≤ 5.0	1.00	Reference		1.00	Reference	
> 5.0	1.84	1.26–2.69	0.002	1.77	1.10–2.87	0.021
Extrapulmonary metastasis						
No	1.00	Reference		1.00	Reference	
Yes	2.26	1.22–4.18	0.010	2.63	1.21–5.72	0.015
DFI after colorectal resection (years)						
≥ 2	1.00	Reference		1.00	Reference	
< 2	1.89	1.28–2.80	0.001	1.62	0.99–2.65	0.056
N stage						
N0	1.00	Reference		1.00	Reference	
N1–2	1.68	1.14–2.48	0.009	1.11	0.69–1.79	0.670
Neoadjuvant therapy						
No	1.00	Reference		1.00	Reference	
Yes	0.49	0.32–0.74	0.001	0.51	0.29–0.88	0.015
Operative procedure						
Wedge resection/segmentectomy	1.00	Reference		1.00	Reference	
Lobectomy	0.77	0.53–1.14	0.193	0.70	0.43–1.15	0.159

DFS disease-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval, *CEA* carcinoembryonic antigen, *DFI* disease-free interval

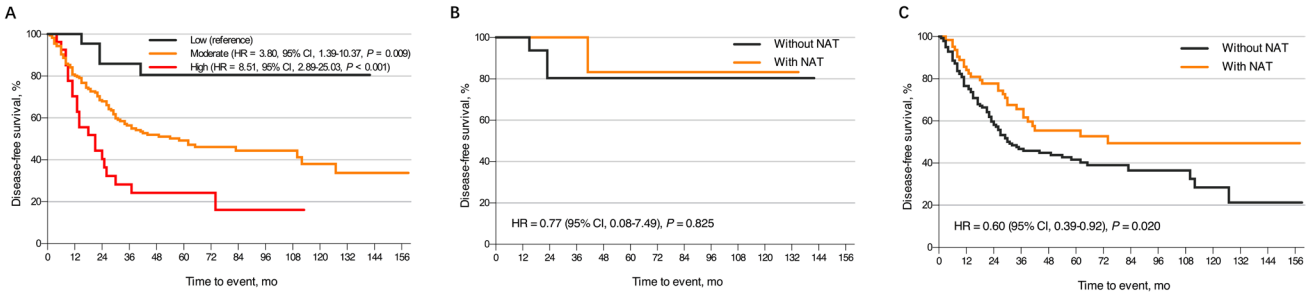

Fig. 2 Survival outcome of patients with CRCPOM stratified by risk group and NAT. **A** DFS for patients with CRCPOM in different risk groups. **B** DFS for CRCPOM patients in low-risk group treated with or without NAT. **C** DFS for CRCPOM patients in high- and moderate-risk group treated with or without NAT. Abbreviations: *CRCPOM* colorectal cancer pulmonary oligometastases, *NAT* neoadjuvant therapy, *DFS* disease-free survival

of individualized therapies. In 2008, the EORTC 40983 (EPOC) trial reported that the combination of perioperative chemotherapy and hepatectomy can safely and effectively improve progression-free survival (PFS) in eligible colorectal liver metastases [21]. Since then, accumulating evidence has supported that the use of NAT could be considered in the individualized treatment of resectable colorectal liver metastases. The proportion of patients with colorectal liver or lung metastases receiving NAT gradually increased from 12.29% in 2010 to 28.31% in 2015 [22]. However, unlike liver metastases, limited data are available regarding the administration of NAT for pulmonary metastases from CRC. Hence, we performed this retrospective study to provide a comprehensive overview of perioperative strategies and to explore the therapeutic value of NAT in patients with CRCPOM.

A recent meta-analysis of 1936 patients demonstrated that perioperative chemotherapy could improve survival in patients with resectable CRCPOM compared with lung metastasectomy alone [23]. Nevertheless, at present, a considerable body of evidence indicates that adjuvant chemotherapy does not appear to increase long-term survival [12–14]. Therefore, we speculated that this survival benefit from perioperative chemotherapy may be conferred

Table 3 Detailed treatment and survival data of patients receiving neoadjuvant therapy

Variable	Number (%)	5-years DFS	*P*-value	HR (95% CI)	*P*-value
Response to preoperative chemotherapy (RECIST 1.1)					
CR	1 (1.4)	76.9%	0.004	1.00 (reference)	
PR	33 (44.6)				
SD	28 (37.8)	45.1%		0.31 (0.13–0.74)	0.008
PD	12 (16.2)				
Lines of NAT					
1 st line	64 (86.5)	56.6%	0.423	1.00 (reference)	
> 1 st line	10 (13.5)	63.0%		0.52 (0.15–1.81)	0.307
Number of cycles					
≤ 4	37 (50.0)	65.5%	0.573	1.00 (reference)	
> 4	37 (50.0)	55.0%		1.01 (0.47–2.15)	0.983
Targeted therapy					
No	54 (73.0)	59.7%	0.628	1.00 (reference)	
Yes	20 (27.0)	52.6%		0.61 (0.27–1.39)	0.239
Risk groups					
Low (0 risk factor)	6 (8.1)	83.3%	0.055	1.00 (reference)	
Moderate (1–2 risk factor)	56 (75.7)	61.6%		2.08 (0.27–16.12)	0.485
High (3–4 risk factors)	12 (16.2)	38.1%		4.74 (0.56–40.31)	0.154

DFS disease-free survival, *HR* hazard ratio, *CI* confidence interval, *RECIST* Response Evaluation Criteria in Solid Tumors, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NAT* neoadjuvant therapy

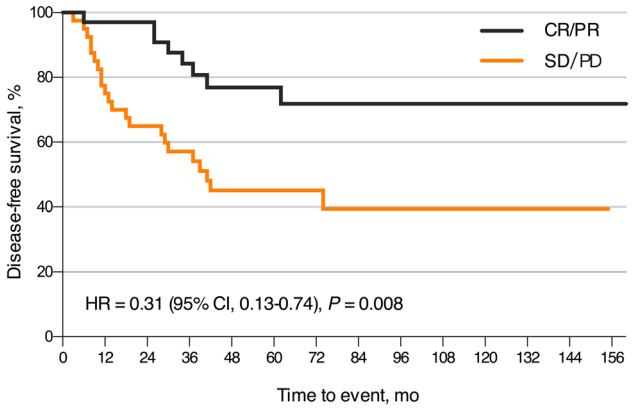

Fig. 3 Kaplan-Meier survival curves for patients receiving NAT stratified by RECIST-defined response. Abbreviations: *NAT* neoadjuvant therapy, *RECIST* Response Evaluation Criteria in Solid Tumors

by the incorporation of neoadjuvant (preoperative) chemotherapy. Indeed, only a few studies with small sample sizes have attempted to determine the role of neoadjuvant chemotherapy in the perioperative setting [12, 24]. Hawkes et al. reported a 5-year relapse-free survival rate of 38% for patients with CRCPOM receiving perioperative chemotherapy ($n = 38$) and 18% for those receiving lung metastasectomy alone ($n = 13$, P value not reported) [24]. Notably, the majority of these patients initially received neoadjuvant chemotherapy with or without targeted agents ($n = 30$), and only 8% of the patients exhibited PD during NAT. In our study, of the 74 patients who underwent NAT, 12 patients (16.2%) had disease progression. The 5-year DFS and OS rates of patients who received NAT were 59.6% and 76.3%, respectively, which were significantly higher than those receiving upfront lung metastasectomy (43.3% and 68.2%) (DFS: HR, 0.49; $P = 0.001$; OS: HR, 0.51; $P = 0.015$), in line with previous findings [7, 24]. Furthermore, similar results were observed after PSM in our study, thereby suggesting that NAT may be an effective strategy for improving prognosis and could be considered in the comprehensive treatment of resectable CRCPOM. Similar to colorectal liver metastases, the implementation of NAT for resectable CRCPOM could potentially eliminate micrometastases, provide early detection of disease progression, facilitate the resectability of pulmonary oligometastases, and assess tumor biological behavior [3, 15].

For resectable CRCPOM, the goal of NAT is to increase the possibility of R0 resection and reduce the risk of postoperative recurrence. However, NAT appears to serve as a double-edged sword in resectable CRCPOM, as this approach may confer chemotherapy-induced toxicity, the increased risk of surgical complications, and the disappearance of metastatic lesions using preoperative imaging [15]. Therefore, it should be emphasized that the importance of the clinical identification of individuals who are suitable for initial NAT. To date, several prognostic factors for poor survival after lung metastasectomy for resectable CRCPOM have been reported in previous studies, including CEA

levels > 5 ng/mL, short DFI (< 2 years), advanced primary tumor stage, multiple metastatic lesions, large tumor size, rectal cancer, older age, multiple metastatic lesions, hilar or mediastinal lymph node involvement, and R1/R2 resection [3]. However, to our knowledge, no prior study has provided an effective and easy-to-use clinical model to predict the risk of recurrence and select appropriate patients for NAT. The present study identified CEA levels > 5 ng/mL, short DFI, extrapulmonary metastases, and lymph node–positive primary tumors as independent predictors of increased risk for recurrence. Based on the abovementioned predictors, we proposed a DFS prediction model to reflect malignant biological behavior and initial tumor burden, which is different from previous models that have been used to predict OS [10, 25]. Patients were stratified into low-risk (0 risk factors), moderate-risk (1–2 risk factors), or high-risk (3–4 risk factors) subgroups, with significant differences in 5-year DFS (79.5%, 48.8%, and 24.2%, respectively). Further analysis indicated that patients with resectable CRCPOM in the moderate- or high-risk subgroups, but not those in the low-risk subgroup, could benefit from NAT. Importantly, these results support the potential clinical application of our risk score for patient selection for NAT, similar to the clinical risk score (CRS) proposed by Fong et al. for colorectal liver metastases [26].

The choice of treatment regimens for NAT for resectable CRCPOM remains controversial due to the lack of clinical evidence. The majority of our patients received oxaliplatin-based chemotherapy, according to existing guidelines for colorectal liver metastases [6, 16]. Similarly, among 38 patients reported by Hawkes et al., 57.9% of the patients received oxaliplatin-based chemotherapy, 15.8% received irinotecan-based chemotherapy, and 23.7% received additional targeted therapy [24]. In the present study, targeted agents were preoperatively administered in approximately 27.0% of the patients with CRCPOM, with no additional benefit being observed (HR 0.61; $P = 0.239$) (Table 3). For patients with KRAS wild-type resectable colorectal liver metastases, the New EPOC trial demonstrated that the preoperative administration of cetuximab significantly reduced progression-free and overall survival [27]. Thus, caution is warranted when additional targeted agents are used for resectable metastatic colorectal cancer, and further prospective studies are needed to confirm their clinical utility in the preoperative setting.

The clinical assessment of efficacy represents a significant clinical challenge in NAT for resectable CRCPOM. RECIST version 1.1 provides a standardized radiological evaluation criterion for various solid tumors and has been clinically proven to be effective, sufficiently robust, and easy to implement [18]. A recent retrospective study aimed to evaluate the potential value of the RECIST 1.1 criteria in colorectal liver metastases that underwent neoadjuvant chemotherapy. RECIST-defined response was reported to be significantly associated with tumor recurrence in the standard chemotherapy group, whereas no significant change was observed for patients receiving bevacizumab-containing chemotherapy [28]. However, the role of the RECIST 1.1 criteria in patients with CRCPOM who underwent NAT has not been reported thus far. In this study, via the CT-based RECIST 1.1 criteria, 46% of the patients achieved either CR (one patient) or PR (33 patients) after NAT. Further survival analysis revealed that the RECIST-defined response was correlated with improved DFS (HR 0.31; $P = 0.008$) (Fig. 3). Likewise, the RECIST 1.1 criteria have also been shown to be valuable in evaluating treatment efficacy and predicting prognosis in patients with resectable non-small cell lung cancer after neoadjuvant chemotherapy [29]. These findings provide evidence to suggest that the RECIST 1.1 criteria have potential clinical application value for the assessment of the efficacy of NAT and adjustments of NAT regimens.

There are several limitations that merit consideration in the present study. First, as a single-center retrospective study conducted over a long time period, it has some inherent limitations, including the heterogeneity of the study population, selection bias, and unmeasured confounders (e.g., detailed chemotherapy regimens and cycles). In the future, prospective randomized control trials should be conducted to confirm the results of our study. Second, limited information regarding surgical complications, as well as the toxic side effects of chemotherapeutic drugs, is available. Therefore, these potentially negative effects of NAT were not fully explored in our study. Moreover, the majority of the patients included in our study did not receive FDG-PETCTT scans, which may have contributed to the underdiagnosis of resectable CRCPOM. Third, for analyses of exposure to NAT, the sample size was not sufficient to compare the efficacies of different neoadjuvant chemotherapy regimens. The standard regimens of NAT remain to be further investigated.

Conclusions

NAT combined with lung metastasectomy could improve long-term survival and increase the chance of cure in patients with resectable CRCPOM. An effective and easy-to-use clinical risk score for predicting recurrence after lung resection was proposed to select suitable patients for initial NAT. Patients with high-risk and moderate-risk are good candidates for preoperative therapy. The chest CT-based RECIST 1.1 criteria is deemed applicable for use in the assessment of the clinical efficacy of NAT.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00384-025-04986-8.

Author contributions Y-P.Z., D-N.M., and Y-B.C. conceived and designed the study. Y-B.C., Y-X.S. and G-H.X. collected and analyzed

the data. Y-B.C. and G-H.X. drafted the manuscript. Y-P.Z. and D-N.M. critically revised the manuscript. Y-B.C. and G-H.X. prepared tables and figures. All authors have reviewed and approved the final submitted version of the manuscript.

Funding This study was supported by the Basic Public Welfare Research Project of Zhejiang Province (grant LTGY23H160044), the Medical Science and Technology Project of Zhejiang Province (grant 2023KY567), and the Traditional Chinese Medicine Science and Technology of Zhejiang Province (grant 2024ZL026).

Data availability The data that support the findings of this study are available on request from the corresponding author.

Declarations

Ethics approval and consent to participate This study utilized anonymized medical records obtained from Zhejiang Cancer Hospital. Informed consent was waived by the Ethics Committee of Zhejiang Cancer Hospital (approval number: IRB-2025–23 (IIT)) as the data were fully de-identified and contained no personally identifiable information. All data processing adhered to institutional guidelines for protecting participant privacy.

Consent for publication Consent for publication was obtained from all authors.

Competing interests The authors declare no competing interests.

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