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Survival Outcomes According to Metastatic Burden and Curative-Intent Resection in Metastatic Colorectal Cancer: a Retrospective Cohort study

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Abstract

Background

Metastatic colorectal cancer (mCRC) encompasses a heterogeneous spectrum of disease presentations. Although advances in surgery and systemic therapy have expanded the technical feasibility and clinical indication of metastasectomy, identifying patients who are most likely to derive oncologic benefit from curative-intent resection (CIR) remains an important clinical challenge. This study evaluated survival outcomes according to metastatic burden, resection status, and treatment strategy in patients with mCRC.

Methods

In this single-center retrospective cohort study, patients diagnosed with mCRC between 2013 and 2023 who underwent surgery and/or chemotherapy were reviewed. Metastatic burden (MB) was stratified into three categories based on the number of metastatic lesions and the number of involved organs: low MB (≤ 3 metastases confined to a single organ), intermediate MB (4–6 metastases in a single organ or 2–6 metastases involving two organs), and high MB (≥ 7 metastases or involvement of three or more organs). Survival outcomes were compared according to MB and resection status. Among patients undergoing CIR (R0 or R1), upfront chemotherapy versus upfront surgery was compared in the low and intermediate MB groups, while in the high MB group, outcomes were compared according to whether CIR was achieved.

Results

MB and resection completeness were strongly associated with survival, with a graded relationship observed across categories. Survival was significantly worse in patients with seven or more metastatic lesions or three or more involved organs. While no significant difference was observed between upfront chemotherapy and upfront surgery in the low MB group, upfront chemotherapy was associated with more favorable outcomes in the intermediate MB group. In the high MB group, achievement of CIR was associated with significantly better survival than no CIR, regardless of treatment sequence.

Conclusions

These findings suggest that CIR could be considered for patients with up to six lesions and two organs and may also be beneficial even in patients with high MB, even when the outcome was R1 resection. Therapeutic strategy should be individualized, and the oncologic benefit of CIR should be discussed within a multidisciplinary framework.

Background

Metastatic colorectal cancer (mCRC) encompasses a heterogeneous spectrum of disease presentations, ranging from limited metastases amenable to radical resection to extensive disseminated disease. Radical resection remains the only potentially curative treatment for mCRC and can provide substantial long-term survival benefit in appropriately selected patients. Recent advances in surgical techniques have expanded technical feasibility and clinical indication for metastasectomy (1). Furthermore, advances in systemic chemotherapy and biologic agents have enabled conversion strategies, allowing a subset of patients with initially unresectable disease to undergo potentially curative-intent resection (CIR) (2). Consequently, an increasing number of patients are being considered for multidisciplinary treatment strategies incorporating CIR.

However, technical feasibility alone does not necessarily translate into meaningful oncologic benefit. Although, some patients achieve durable disease control following curative-intent treatment, others experience early recurrence despite technically successful resection (3). These observations suggest that additional factors beyond technical resectability should be considered when selecting candidates for curative-intent treatment.

Therefore, identifying patients who are most likely to derive oncologic benefit from CIR remains an important clinical challenge. Patients with mCRC are often broadly categorized as resectable, potentially or borderline resectable, and unresectable according to disease extent and anticipated treatment strategy (4). However, no universally accepted definitions exist, and such classifications do not fully capture the biological and clinical heterogeneity of mCRC (5). Furthermore, resectability status may evolve throughout the course of treatment, and treatment decisions should consider not only technical feasibility but also the anticipated oncologic benefit of CIR (6). Even when the number of metastatic lesions is identical, resectability may vary according to their anatomical distribution, and the oncologic benefit of resection may differ according to tumor biology; for these reasons, resectability criteria are difficult to define precisely, and individualized decision-making through a multidisciplinary team (MDT) is considered appropriate. Nevertheless, quantitative measures of disease burden may still offer a fundamental and useful reference point for this individualized decision-making. Among the various prognostic factors, metastatic burden (MB) has consistently been associated with oncologic outcomes in patients with mCRC. Both the number of metastatic lesions and the number of involved organs influence long-term survival and the potential benefit derived from surgical treatment (7, 8). Nevertheless, the prognostic significance of these factors and their role in identifying patients most likely to benefit from CIR remain incompletely defined.

Therefore, this study evaluated survival outcomes according to MB, resection status, and treatment strategy in patients with mCRC. We further investigated whether metastatic burden stratification (MBS) based on the number of metastatic lesions and the number of involved organs could help identify patients most likely to derive meaningful oncologic benefit from CIR.

Methods

Study Design and Patient Population

This retrospective, single-center observational cohort study was conducted at Chungnam National University Hospital, a tertiary academic medical center in South Korea. The study included patients diagnosed with mCRC between January 2013 and December 2023. This study was approved by the Institutional Review Board (Medical Research Ethics Review Committee) of Chungnam National University Hospital (IRB No. 2026-01-051), which waived the requirement for written informed consent due to the retrospective design of the study, in accordance with institutional guidelines and the Declaration of Helsinki.

Patient Selection

Inclusion criteria were as follows: histologically confirmed colorectal cancer; primary tumor amenable to complete resection; receipt of anti-cancer treatment, including surgical resection and/or systemic chemotherapy; and availability of adequate follow-up data. Exclusion criteria were as follows: no anti-cancer treatment received; failure to achieve complete resection of the primary tumor; loss to adequate follow-up; or concurrent malignancies diagnosed during the same period. Synchronous metastasis was defined as metastasis detected at or within 6 months of primary CRC diagnosis, and metachronous thereafter.

Stratification of Metastatic Burden and Resection Status

At the time of initial diagnosis, patients were stratified according to MB based on the number of metastatic lesions and the number of involved organs. Patients with three or fewer metastatic lesions confined to a single organ were classified as having low MB. Patients with 4–6 metastatic lesions in a single organ or 2–6 metastatic lesions involving two organs were classified as having intermediate MB. Patients with seven or more metastatic lesions or involvement of three or more organs were classified as having high MB.

Surgical outcomes were categorized according to resection status. R0 resection was defined as complete resection with histologically negative margins. R1 resection was defined as microscopic residual tumor at the surgical margin, whereas R2 resection indicated macroscopic residual disease. Patients who did not undergo surgery and received systemic chemotherapy alone were classified as the chemotherapy-only group.

Treatment strategy

R0 and R1 resection were classified as the CIR group, as R1 resection typically represents an intention-to-treat outcome of an attempted R0 resection, whereas R2 resection—including palliative resection or diversion—and chemotherapy alone were classified as the no-CIR group.

To evaluate the impact of treatment sequence on clinical outcomes, patients who underwent CIR (R0 or R1) within each MB group were categorized according to their initial treatment approach as either upfront surgery or upfront chemotherapy. Cases receiving surgery only or chemotherapy only were excluded from this analysis. Treatment decisions were made through multidisciplinary discussion involving surgical oncologists, medical oncologists, and radiologists based on MB, anatomical feasibility, treatment response, and individual patient factors.

Study Endpoints

The study endpoints of interest were overall survival (OS) and progression-free survival (PFS). OS was defined as the time from the initial diagnosis of mCRC to death from any cause, while PFS was defined as the time from the initial diagnosis to disease progression or death from any cause, whichever occurred first. Secondary endpoints included comparison of survival outcome according to metastatic burden stratification (MBS), resection status, the number of metastatic lesions, the number of involved organs, and treatment strategy (upfront surgery vs. upfront chemotherapy in low and intermediate MB group, and CIR vs. no CIR in high MB group).

Data collection and Statistical Analysis

Comprehensive clinical, pathological, and treatment-related variables were extracted from electronic medical records via the institutional clinical data warehouse (CDW) system.

Statistical analyses were conducted using SPSS software version 28.0 (IBM Corp., Armonk, NY, USA). Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test, including the log-rank test for trend where the ordering of MB groups was of interest. For the overall cohort analyses (Figs. 1–4), we treated MB, resection status, the number of metastatic lesions, and the number of involved organs as ordered categorical variables and analyzed them using repeated (sequential) contrasts, so that each level was compared with its immediate neighbor. Prognostic factors for OS and PFS were identified through univariate and multivariate analyses using Cox proportional hazards regression modeling within each MB group (Tables 2, 3). Within these models, the number of metastatic lesions and the number of involved organs were similarly treated as ordered categorical variables using repeated (sequential) contrasts, whereas resection status was reclassified into CIR (R0 or R1), R2 resection, and chemotherapy alone, given the limited sample size within each MB group; CIR served as the reference category, and R2 and chemotherapy alone were each compared against it using indicator contrasts. Proportional hazard assumptions were evaluated, and a two-sided p-value < 0.05 was considered statistically significant for all analyses. Continuous variables were compared using the independent t-test or one-way ANOVA for normally distributed data, and the Mann-Whitney U test or

Kruskal-Wallis test for non-normally distributed data, with normality assessed using the Shapiro-Wilk test; categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

Table 2
Univariate Cox regression analyses for survival outcomes

Low metastatic burden group				
	Progression-free survival		**Overall survival**	
Variable	HR (95% CI)	p-value	HR (95% CI)	P-value
Age (> 75 vs ≤ 75)	1.288 (0.735–2.260)	0.377	2.360 (1.339–4.161)	0.003
Sex (female vs male)	1.235 (0.839–1.820)	0.285	1.146 (0.735–1.787)	0.548
ASA (3–4 vs 1–2)	0.981 (0.496–1.943)	0.957	1.521 (0.757–3.053)	0.238
Primary tumor side (Lt vs Rt)	1.364 (0.853–2.181)	0.195	1.371 (0.760–2.473)	0.295
Preop CEA (> 5 vs ≤ 5)	1.578 (1.071–2.325)	0.021	1.105 (0.713–1.714)	0.654
Timing (Synchronous vs Metachronous)	1.246 (0.842–1.842)	0.271	1.247 (0.786–1.979)	0.349
Resection status Chemotherapy only vs R0/R1	2.506 (0.920–6.830)	0.072	2.608 (0.816–8.339)	0.106
Number of metastatic lesions	N/A		N/A	
Number of involved organs	N/A		N/A	
Intermediate metastatic burden group				
	Progression-free survival		**Overall survival**	
Variable	HR (95% CI)	p-value	HR (95% CI)	P-value
Age (> 75 vs ≤ 75)	1.858 (0.793–4.354)	0.154	2.834 (1.193–6.729)	0.018
Sex (female vs male)	0.870 (0.376–2.012)	0.746	0.372 (0.109–1.273)	0.115
ASA (3–4 vs 1–2)	1.091 (0.377–3.155)	0.872	1.387 (0.399–4.820)	0.607
Primary tumor side (Lt vs Rt)	0.682 (0.258–1.804)	0.441	0.602 (0.198–1.830)	0.371
Preop CEA (> 5 vs ≤ 5)	1.189 (0.594–2.377)	0.625	1.108 (0.485–2.531)	0.809

Low metastatic burden group				
	Progression-free survival		**Overall survival**	
Timing (Synchronous vs Metachronous)	0.859 (0.405–1.819)	0.691	0.495 (0.215–1.138)	0.098
Resection status R2 vs R0/R1 Chemotherapy only vs R0/R1	2.222 (0.657–7.511) 1.873 (0.701–5.003)	0.248 0.199 0.210	3.182 (0.873–11.598) 5.200 (1.659–16.304)	0.011 0.079 0.005
Number of metastatic lesions 4–6 lesions vs 2–3 lesions	0.267 (0.113–0.633)	0.003	0.252 (0.098–0.650)	0.004
Number of involved organs 2 organs vs 1 organ	1.631 (0.802–3.322)	0.177	2.198 (0.947–5.102)	0.067
High metastatic burden group				
	Progression-free survival		**Overall survival**	
Variable	HR (95% CI)	p-value	HR (95% CI)	P-value
Age (> 75 vs ≤ 75)	1.330 (0.863–2.050)	0.197	1.249 (0.819–1.905)	0.302
Sex (female vs male)	1.134 (0.745–1.725)	0.557	1.107 (0.722–1.698)	0.640
ASA (3–4 vs 1–2)	1.100 (0.635–1.905)	0.734	1.106 (0.648–1.886)	0.713
Primary tumor side (Lt vs Rt)	0.999 (0.683–1.462)	0.997	0.877 (0.595–1.295)	0.510
Preop CEA (> 5 vs ≤ 5)	0.842 (0.576–1.231)	0.375	1.098 (0.746–1.616)	0.635
Timing (Synchronous vs Metachronous)	1.028 (.662-1.598)	0.901	0.760 (0.487–1.185)	0.226
Resection status R2 vs R0/R1 Chemotherapy only vs R0/R1	1.899 (1.191–3.029) 1.984 (1.192–3.303)	0.012 0.007 0.008	3.219 (1.886–5.495) 4.545 (2.528–8.170)	< 0.001 < 0.001 < 0.001
Number of metastatic lesions	N/A		N/A	

Low metastatic burden group				
	Progression-free survival		**Overall survival**	
Number of involved organs	1.085 (0.706–1.667)	0.003	1.880 (1.206–2.933)	< 0.001
2 organs vs 1 organ		0.712		
3 organs vs 2 organs	5.051 (1.890-13.514)	0.001	2.375 (0.908–6.211)	0.005
				0.078
≥ 4 organs vs 3 organs	0.617 (0.119–3.195)	0.565	1.183 (0.282–4.975)	0.818

Table 3
Multivariate Cox Regression analyses for survival outcomes

Low metastatic burden group				
	Progression-free survival		**Overall survival**	
Variable	HR (95% CI)	p-value	HR (95% CI)	P-value
Age (> 75 vs ≤ 75)	1.324 (0.754–2.326)	0.329	2.447 (1.384–4.326)	0.002
Resection status	2.594 (0.949–7.089)	0.063	3.004 (0.934–9.667)	0.065
Chemotherapy only vs R0/R1				
Intermediate metastatic burden group				
	Progression-free survival		**Overall survival**	
Variable	HR (95% CI)	p-value	HR (95% CI)	P-value
Age (> 75 vs ≤ 75)	0.941 (0.319–2.777)	0.912	1.692 (0.573–5.001)	0.341
Resection status	8.834 (1.032–75.614)	0.063	3.291 (0.641–16.909)	0.006
R2 vs R0/R1	2.304 (0.831–6.385)	0.047		0.154
Chemotherapy only vs R0/R1		0.109	7.324 (2.123–25.265)	0.002
Number of metastatic lesions	12.712 (2.059–78.477)	0.006	5.565 (1.132–27.350)	0.035
4–6 lesions vs 2–3 lesions				
Number of involved organs	3.409 (0.627–18.549)	0.156	1.555 (0.352–6.863)	0.560
2 organs vs 1 organ				
High metastatic burden group				
	Progression-free survival		**Overall survival**	
Variable	HR (95% CI)	p-value	HR (95% CI)	P-value
Age (> 75 vs ≤ 75)	1.367 (0.881–2.119)	0.163	1.243 (.805 – 1.920)	0.326
Resection status	1.825 (1.121–2.973)	0.020	2.772 (1.600-4.803)	< 0.001
R2 vs R0/R1	1.984 (1.178–3.340)	0.016	4.257 (2.348–7.719)	< 0.001
Chemotherapy only vs R0/R1		0.010		< 0.001
Number of involved organs	0.877 (0.560–1.374)	0.006	1.553 (0.991–2.427)	0.007
Figures and legends				

Low metastatic burden group				
	Progression-free survival		**Overall survival**	
2 organs vs 1 organ	5.208 (1.931–14.085)	0.566	2.427 (0.919–6.410)	0.055
3 organs vs 2 organs	0.647 (0.124–3.378)	0.001	0.999 (0.232–4.310)	0.074
≥ 4 organs vs 3 organs		0.605		0.999
Figures and legends				

Results

Patient Characteristics

A total of 467 patients diagnosed with mCRC between January 2013 and December 2023 were screened. After excluding patients who received no treatment (n = 33), failed to achieve complete resection of the primary tumor (n = 39), were lost to follow-up (n = 40), or had concurrent malignancies (n = 4), 351 patients were included in the final analysis.

The median age was 66 years (range, 25–88 years), and 241 patients (68.7%) were male. Synchronous metastases were present in 231 patients (65.8%), while 120 patients (34.2%) developed metachronous metastases. Left-sided primary tumors accounted for 74.6% of cases, with the sigmoid colon and rectum being the most common primary tumor locations.

According to metastatic burden stratification, 184 patients were classified as low burden, 40 as intermediate burden, and 127 as high burden. Surgical treatment was performed in 298 patients (84.9%), including R0 resection in 226 patients (64.4%), R1 resection in 12 patients (3.4%), and R2 resection in 60 patients (17.1%). The remaining 53 patients (15.1%) received systemic chemotherapy alone. For the entire cohort, median progression-free survival (mPFS) and median overall survival (mOS) were 15.3 and 38.9 months, respectively. The clinical characteristics of the entire cohort and subgroup according to MB were described in Table 1.

Table 1
Clinical characteristics according to metastatic burden

Characteristic	Total (N = 351)	Low (N = 184)	Intermediate (N = 40)	High (N = 127)	P-value
Sex	241 (68.7%)	120 (65.2%)	31 (77.5%)	90(70.9%)	0.259
Male	110 (31.3%)	64 (34.8%)	9 (22.5%)	37 (29.1%)	
Female					
Age (mean, range)	65.32 (25–88)	64.18 (25–86)	63.53 (27–81)	67.54 (25–88)	0.015
ASA	308 (87.7%)	166 (90.2%)	34 (85.0%)	108 (87.7%)	0.334
I, II	43 (12.3%)	18 (9.9%)	6 (15.0%)	19 (15.0%)	
III, IV					
Primary location	86 (24.5%)	35 (19.0%)	6 (15.0%)	45 (35.4%)	0.005
Right	262 (74.6%)	147 (79.9%)	34 (85.0%)	81 (63.8%)	
Left	3 (0.9%)	2 (1.1%)	0 (0.0%)	1 (0.8%)	
Multiple					
CEA	153 (43.6%)	82 (44.6%)	20 (50.0%)	51 (40.2%)	0.530
< 5 ng/mL	198 (56.4%)	102 (55.4%)	20 (50.0%)	76 (59.8%)	
> 5 ng/mL					
Timing of metastasis	231 (65.8%)	108 (58.7%)	27 (67.5%)	96 (75.6%)	0.008
Synchronous	120 (34.2%)	76 (41.3%)	13 (32.5%)	31 (24.4%)	
Metachronous					
Resection status	226 (64.4%)	174 (94.6%)	29 (72.5%)	23 (18.1%)	< 0.001
R0	12 (3.4%)	3 (1.6%)	1 (2.5%)	8 (6.3%)	
R1	60 (17.1%)	0 (0.0%)	3 (7.5%)	57 (44.9%)	
R2	53 (15.1%)	7 (3.8%)	7 (17.5%)	39 (30.7%)	
Chemotherapy only					
Preoperative chemotherapy before curative-intent resection (R0 & R1)	(N = 238)	(N = 180)	(N = 30)	(N = 31)	< 0.001
	62 (26.1%)	30 (16.9%)	15 (50%)	17 (54.8%)	

Survival Outcomes According to Metastatic burden stratification

Survival outcomes varied significantly according to MBS ($P < 0.001$ for both PFS and OS), with a graded pattern from low (mPFS 21.9 months, mOS 64.6 months) through intermediate (14.5, 39.3 months) to high MB (11.5, 21.4 months) (Fig. 1).

Survival Outcomes According to Resection Status

Survival outcomes varied significantly by resection status ($P < 0.001$ for both PFS and OS), with a graded pattern from R0 (mPFS 18.9 months, mOS 64.5 months) through R1 (11.5, 20.5 months), R2 (10.4, 19.0 months), to chemotherapy alone (9.1, 13.4 months) (Fig. 2).

Survival Outcomes According to the Number of Metastatic Lesions and Involved Organs

Both the number of metastatic lesions and the number of involved organs were significantly associated with survival. Survival showed a graded pattern according to lesion number, from 1–3 lesions (mPFS 18.9 months, mOS 64.5 months) through 4–6 lesions (20.6, 63.5 months) to ≥ 7 lesions (11.5, 21.4 months) (log-rank test, $p < 0.001$ for both PFS and OS) (Fig. 3). A similar graded pattern was observed according to the number of involved organs, from 1 organ (mPFS 16.4 months, mOS 48.1 months) through 2 organs (11.8, 19.7 months) and 3 organs (5.1, 12.7 months) to ≥ 4 organs (5.6, 10.7 months) ($P < 0.001$ for both PFS and OS) (Fig. 4).

Impact of Treatment Strategy: Upfront Chemotherapy vs. Upfront Surgery

To further assess the prognostic impact of treatment strategy, we compared upfront chemotherapy and upfront surgery among patients who underwent CIR, stratified by MB group. In the low MB group, no significant difference in PFS or OS was observed between upfront chemotherapy and upfront surgery (mPFS 18.1 vs. 23.4 months, $P = 0.224$; mOS 65.1 vs. 64.6 months, $P = 0.468$) (Fig. 5). Among intermediate MB patients undergoing CIR ($n = 30$), upfront chemotherapy showed a trend toward longer PFS and OS than upfront surgery (mPFS 21.9 vs. 13.3 months, $P = 0.073$; mOS 68.7 vs. 38.9 months, $P = 0.209$), although the difference did not reach statistical significance (Fig. 6). In the high MB group, no significant difference was observed between upfront chemotherapy and upfront surgery (mPFS 16.7 vs. 14.3 months, $P = 0.842$; mOS 53.8 vs. 36.5 months, $P = 0.801$); given the small number of events occurring early in the follow-up period in this group, the corresponding survival curves are not shown.

Impact of Curative-Intent Resection in the High MB Group

Within the high MB group, patients who underwent CIR had significantly better PFS and OS than those who did not undergo CIR, (mPFS 14.2 vs. 10.1 months, P = 0.002; mOS 50.2 vs. 16.2 months, P < 0.001) (Fig. 7).

Prognostic Factors by MB Group

On univariate analysis (Table 2), in the low MB group, older age (> 75 years) was associated with significantly worse OS (HR 2.360, 95% CI 1.339–4.161, P = 0.003), and elevated preoperative CEA (> 5 ng/mL) was associated with significantly worse PFS (HR 1.578, 95% CI 1.071–2.325, P = 0.021). Resection status was not significantly associated with either outcome in this group (PFS P = 0.072, OS P = 0.106), and no R2 cases were present. In the intermediate MB group, older age was associated with significantly worse OS (HR 2.834, 95% CI 1.193–6.729, P = 0.018). Resection status showed no significant association with PFS (global P = 0.248), but chemotherapy alone was associated with significantly worse OS than CIR (HR 5.200, 95% CI 1.659–16.304, P = 0.005). Patients with 4–6 metastatic lesions had significantly better PFS (HR 0.267, 95% CI 0.701–5.003, P = 0.003) and OS (HR 0.252, 95% CI 0.098–0.650, P = 0.004) than those with 2–3 lesions, whereas involvement of 2 organs versus 1 organ showed no significant difference in either outcome (PFS P = 0.177, OS P = 0.067). In the high MB group, both R2 resection (PFS HR 1.899, 95% CI 1.191–3.029, P = 0.007; OS HR 3.219, 95% CI 1.886–5.495, P < 0.001) and chemotherapy alone (PFS HR 1.984, 95% CI 1.192–3.303, P = 0.008; OS HR 4.545, 95% CI 2.528–8.170, P < 0.001) were associated with significantly worse outcomes than CIR. Involvement of 2 organs versus 1 was associated with significantly worse OS (HR 1.880, 95% CI 1.206–2.933, P = 0.005) but not PFS (P = 0.712), whereas involvement of 3 organs versus 2 was associated with significantly worse PFS (HR 5.051, 95% CI 1.890–13.514, P = 0.001) but not OS (P = 0.078); the comparison between 3 and 4 or more organs showed no significant difference in either outcome (PFS P = 0.565, OS P = 0.818).

On multivariable analysis (Table 3), in the low MB group, older age remained independently associated with worse OS (HR 2.447, 95% CI 1.384–4.326, P = 0.002), whereas resection status was no longer significantly associated with either outcome (PFS P = 0.063, OS P = 0.065). In the intermediate MB group, R2 resection was independently associated with significantly worse PFS than CIR (HR 8.834, 95% CI 1.032–75.614, P = 0.047), and chemotherapy alone was independently associated with significantly worse OS than CIR (HR 7.324, 95% CI 2.123–25.265, P = 0.002). Patients with 4–6 lesions continued to show significantly worse PFS (HR 12.712, 95% CI 2.059–78.477, P = 0.006) and OS (HR 5.565, 95% CI 1.132–27.350, P = 0.035) than those with 2–3 lesions, while organ involvement (1 vs. 2) remained non-significant (PFS P = 0.156, OS P = 0.560). In the high MB group, both R2 resection (PFS HR 1.825, 95% CI 1.121–2.973, P = 0.016; OS HR 2.772, 95% CI 1.600–4.803, P < 0.001) and chemotherapy alone (PFS HR 1.984, 95% CI 1.178–3.340, P = 0.010; OS HR 4.257, 95% CI 2.348–7.719, P < 0.001) remained independently associated with significantly worse PFS and OS than CIR. Among involved-organ comparisons, only the difference between 2 and 3 organs remained significant, and only for PFS (HR 5.208, 95% CI 1.931–14.085, P = 0.001); the comparisons between 1 and 2 organs (PFS P = 0.566, OS P

= 0.055), and between 3 and 4 or more organs (PFS P = 0.605, OS P = 0.999), were not significant for either outcome.

Discussion

In this single-center retrospective cohort of 351 patients with mCRC, survival was associated with MB, resection status, and treatment sequencing. Patients with low MB had the most favorable outcomes. Within the intermediate MB group, patients with 4–6 metastatic lesions appeared to have more favorable survival than those with 2–3 lesions on univariate analysis, but this association reversed after adjusting for resection status, suggesting that it was confounded by a higher rate of CIR in the 4–6 lesion subgroup, which predominantly comprised single-organ (typically hepatic) disease. Patients with seven or more lesions or three or more involved organs had substantially worse survival. Resection status followed a graded pattern, with R0 resection associated with the longest survival, followed by R1 resection, R2 resection, and chemotherapy alone. Among patients selected for CIR, upfront chemotherapy was associated with a survival trend favoring conversion therapy in the intermediate MB group, whereas no such difference was observed in the low MB group. In the high MB group, patients who achieved CIR had significantly better survival than those who did not, regardless of treatment sequence.

Metastatic colorectal cancer is conventionally categorized as resectable, potentially or borderline resectable, or unresectable, but no precise, universally accepted definition exists for these categories, and in clinical practice, treatment strategy for each patient is individualized through multidisciplinary team (MDT) discussion rather than derived from fixed anatomical criteria. Within this context, the intent of the present study is not to redefine resectability or to establish definitive surgical indication criteria for mCRC. Rather, our results are intended to provide supportive evidence to help identify, particularly within the intermediate and high MB groups, which patients are more likely to benefit from CIR, and which are not, thereby helping to avoid both undertreatment and overtreatment. The MBS framework used in this study was based solely on the quantitative burden of disease—namely, the number of metastatic lesions and the number of involved organs—and did not capture anatomical factors that also influence resectability, such as the proximity of lesions to major vascular structures or their spatial distribution (e.g., clustered within a single hepatic lobe or an organ versus scattered in both hepatic lobes or multiple organs), both of which require individualized assessment by the MDT.

With respect to MB, our data lend some support to actively exploring the possibility of CIR even in patients with a moderately high burden of disease, given that survival was broadly comparable between those with 1–3 and 4–6 metastatic lesions in the overall cohort. However, once MB reached seven or more lesions or involved three or more organs, survival dropped substantially, suggesting that the anticipated oncologic benefit of resection should be weighed more critically, rather than pursued as readily, in this subgroup. This threshold effect is also consistent with reports that extension of metastatic disease to additional organs, including extrahepatic and nodal sites, consistently portends a worse prognosis in mCRC (9). Within the intermediate MB group specifically, the number of metastatic

lesions remained significantly and independently associated with both PFS and OS on multivariable analysis, with a higher hazard observed in patients with 4–6 lesions relative to those with 2–3 lesions. Notably, on univariate analysis, patients with 4–6 lesions had shown more favorable outcomes, an association that reversed once CIR was accounted for on multivariable analysis; this suggests that the survival of patients with 4–6 lesions may in part be driven by the receipt of CIR, indicating that outcomes in this subgroup can still be meaningfully improved through CIR. Within the high MB group, the number of involved organs remained significantly associated with both outcomes, with a significant increase in hazard specifically between three and two organs, suggesting that among patients with high MB, those with fewer involved organs may still be reasonable candidates for CIR. Nevertheless, even within the high MB group, patients who achieved CIR had better outcomes than those who did not, suggesting that although the decision should be made cautiously, the possibility of CIR should not be entirely excluded even in this subgroup. Taken together, these findings suggest that CIR may reasonably be considered up to six lesions or two involved organs, and that its possibility should also be considered even in the high MB group.

With respect to resection status, survival followed a graded pattern across resection categories, with the clearest separation between R0 (median PFS 18.9 months, OS 64.5 months) and R1 resection (11.5, 20.5 months), a smaller, though still directionally consistent, difference between R1 and R2 resection (10.4, 19.0 months), and the poorest outcomes observed with chemotherapy alone (9.1, 13.4 months). On multivariable analysis, no significant difference was observed between CIR and chemotherapy alone in the low MB group (OS P = 0.065)—the only comparison possible in this subgroup, as no R2 cases were present. In the intermediate MB group, chemotherapy alone was associated with significantly worse OS than CIR (HR 7.324, 95% CI 2.123–25.265, P = 0.002), whereas the comparison between R2 and CIR was associated with a wide confidence interval, reflecting the small number of R2 cases (n = 3) in this subgroup. In the high MB group, CIR (R0 or R1) was associated with significantly better survival than either R2 resection or chemotherapy alone (R2 vs. CIR: OS HR 2.772, 95% CI 1.600–4.803, P < 0.001; chemotherapy alone vs. CIR: OS HR 4.257, 95% CI 2.348–7.719, P < 0.001). Notably, although patients with high MB had substantially worse survival than those with lower MB overall, achievement of CIR was associated with a marked survival advantage even within this subgroup (mPFS 14.2 vs. 10.1 months, log-rank P = 0.002; mOS 50.2 vs. 16.2 months, log-rank P < 0.001) (Fig. 6), reinforcing the importance of careful patient selection rather than burden-based exclusion from curative-intent treatment. This finding is consistent with data from the larger, prospective RAXO study, in which patients undergoing R0 or R1 resection had a median overall survival of 80.4 months, compared with 39.1 months for R2 resection or local ablative therapy and 20.8 months for systemic therapy alone, indicating that R1 resection, when grouped with R0, still conferred a substantial survival advantage over more limited local control or systemic therapy alone (10). Although current guidelines for mCRC state that only complete resection provides a survival benefit (11), several recent studies of liver metastases have reported that R1 resection, or a positive margin, does not significantly affect overall survival (12–14). These findings raise the question of whether surgery should be pursued only when R0 resection is achievable. A parallel can be drawn with the evolving standard for local treatment intensity in colorectal liver metastases more

broadly: whereas anatomically complete resection was historically regarded as the only adequate local treatment, more recent evidence, including the phase 3 COLLISION trial, has shown that thermal ablation is non-inferior to surgical resection in overall survival for small, resectable liver metastases, reflecting how advances in local ablative techniques, radiotherapy, and systemic therapy have progressively relaxed the threshold considered necessary for adequate local disease control (15). A related concept applies to peritoneal metastases, where cytoreductive surgery is intended to achieve macroscopic clearance of disease, while HIPEC is designed to control residual microscopic disease that surgery alone cannot remove (16). By extension, this therapeutic principle—that residual microscopic disease may be controlled by adjunct chemotherapy even when resection is macroscopically complete but microscopically incomplete—supports the notion that R1 resection, while not equivalent to R0, may still offer an oncologic benefit over R2 resection or chemotherapy alone. Taken together, these observations suggest that although R1 resection is associated with worse outcomes than R0 resection, it may still improve survival compared with chemotherapy alone. This implies that CIR should not be limited only to patients in whom R0 resection is certain. Rather, with appropriate patient selection, active pursuit of resection—achieving R0 when possible, or at least R1 when not—may still provide a survival benefit. Nonetheless, our own R1 subgroup was small (12 patients in the overall cohort), and the number of R2 cases within the intermediate MB group was similarly limited (n = 3); these observations may reflect a similar trend to that seen in other studies but cannot serve as independent confirmation and should be interpreted with caution.

With respect to treatment sequencing, no difference in outcome was observed between upfront chemotherapy and upfront surgery in the low MB group, whereas patients in the intermediate MB group had better outcomes with upfront chemotherapy. This pattern is consistent with existing evidence. In the EORTC 40983 trial, perioperative FOLFOX4 improved progression-free survival in patients with resectable liver metastases, but this did not translate into an overall survival benefit on long-term follow-up (17, 18), and subsequent analyses have suggested that neoadjuvant therapy offers limited, patient-dependent value in clearly resectable disease (19). Given the possibility of chemotherapy-related hepatotoxicity, transient immune suppression, and increased surgical complications associated with anti-VEGF antibody therapy, upfront resection may be a reasonable strategy for patients with low MB. In contrast, a randomized phase II trial showed that conversion treatment improved overall survival specifically in patients with higher CEA levels or more than two liver metastases (20). Consistent with this, in the intermediate MB group, upfront chemotherapy may allow tumor biology and treatment response to be assessed, potentially improving outcomes.

This study has several limitations. Its single-center, retrospective design is subject to selection bias, and treatment was not randomly assigned, which particularly limits the comparison of treatment sequences. The size of the intermediate-burden treatment-strategy subgroup (n = 30) was small, reducing statistical power for this comparison. Similarly, the number of R2 cases within the intermediate MB group (n = 3) was small, rendering the corresponding multivariable estimate for R2 versus CIR unstable. The MBS framework was based solely on lesion number and organ count and did not incorporate anatomical factors relevant to resectability, such as the proximity of lesions to major vascular structures or their

spatial distribution. Molecular markers such as RAS, BRAF, and microsatellite instability status were not available, limiting biological characterization of the cohort. Finally, the thresholds used for metastatic burden stratification were defined within this dataset and require external validation. Prospective, multicenter studies incorporating molecular profiling will be needed to confirm the proposed stratification and to refine patient selection for curative-intent surgery. Nonetheless, given the broad clinical spectrum of mCRC and the need for a highly individualized treatment approach, conducting a randomized controlled trial would be practically challenging, and this retrospective analysis may still offer meaningful evidence to inform clinical decision-making.

Conclusions

MB and resection completeness were strongly associated with survival, with a graded relationship observed across categories. These findings suggest that CIR could be considered for patients with up to six lesions and two organs and may also be beneficial even in patients with high MB, even when the outcome was R1 resection. Therapeutic strategy should be individualized, and the oncologic benefit of curative-intent resection should be discussed within a multidisciplinary framework. Further evidence is needed to better identify patients with mCRC who are most likely to benefit from CIR.

Abbreviations

mCRC
metastatic colorectal cancer
CIR
curative-intent resection
MB
metastatic burden
R0
complete resection with negative margins
R1
resection with microscopic residual disease
MDT
multidisciplinary team
MBS
metastatic burden stratification
IRB
Institutional Review Board
ASA
American Society of Anesthesiologists
R2
resection with macroscopic residual disease
OS

overall survival
PFS
progression-free survival
HR
hazard ratio
CI
confidence interval
CEA
carcinoembryonic antigen
HIPEC
hyperthermic intraperitoneal chemotherapy
VEGF
vascular endothelial growth factor
RAS
rat sarcoma virus gene
BRAF
B-Raf proto-oncogene.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (Medical Research Ethics Review Committee) of Chungnam National University Hospital (IRB No. 2026-01-051), which waived the requirement for written informed consent due to the retrospective design of the study, in accordance with institutional guidelines and the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Declarations

Declarations of Generative AI and AI-assisted technologies in the writing process

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Author Contribution

IY contributed to statistical analysis and manuscript writing. DK contributed to data curation and analyses. JK. contributed to study design and data interpretation. KL. contributed to study design, statistical analysis, and manuscript writing. All authors read and approved the final manuscript.

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Not applicable

Data Availability

The datasets generated and/or analysed during the current study are not publicly available due to patient privacy concerns but are available from the corresponding author on reasonable request.

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Figures

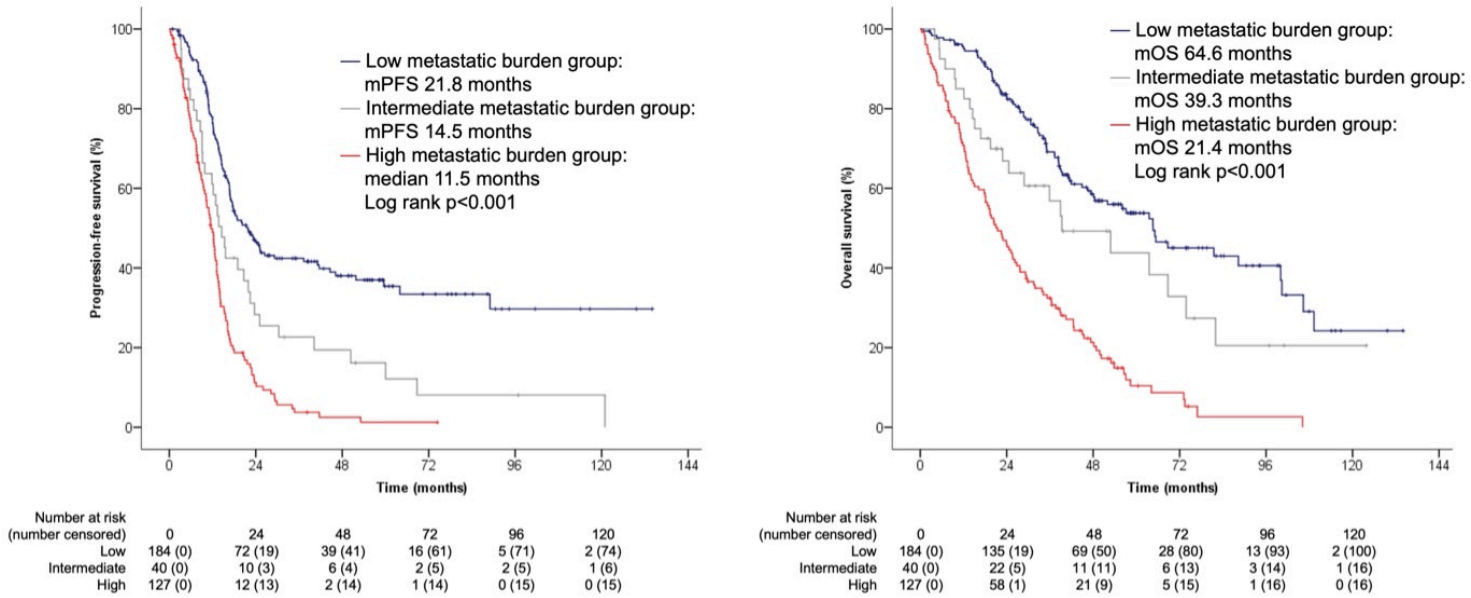


Figure 1

Progression-free survival and overall survival by metastatic burden stratification

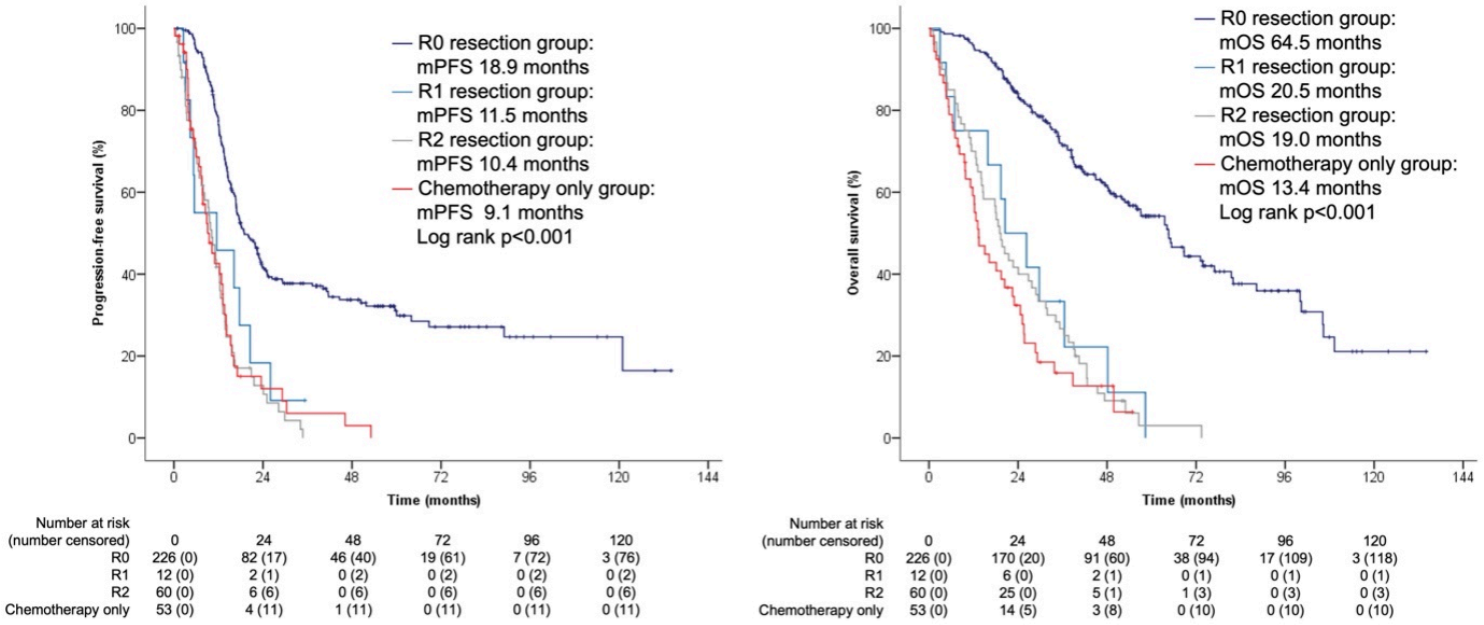
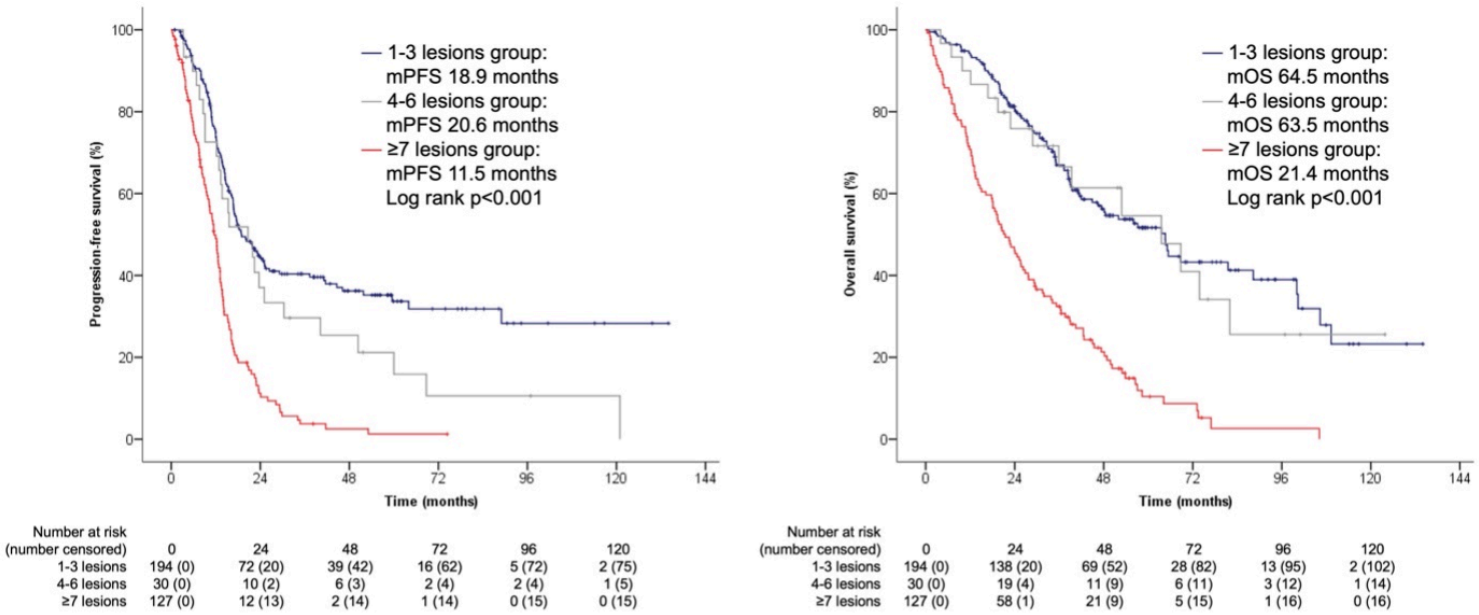


Figure 2

Progression-free survival and overall survival by to resection status

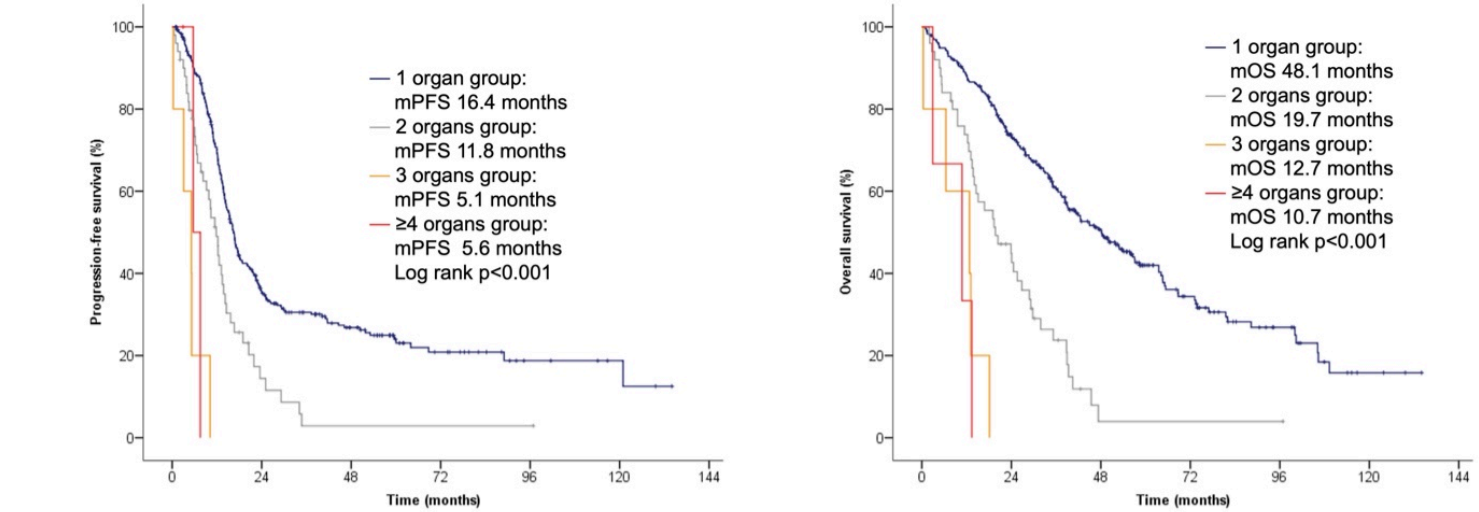


Number at risk (number censored)	0	24	48	72	96	120
1-3 lesions	194 (0)	72 (20)	39 (42)	16 (62)	5 (72)	2 (75)
4-6 lesions	30 (0)	10 (2)	6 (3)	2 (4)	2 (4)	1 (5)
≥7 lesions	127 (0)	12 (13)	2 (14)	1 (14)	0 (15)	0 (15)

Number at risk (number censored)	0	24	48	72	96	120
1-3 lesions	194 (0)	138 (20)	69 (52)	28 (82)	13 (95)	2 (102)
4-6 lesions	30 (0)	19 (4)	11 (9)	6 (11)	3 (12)	1 (14)
≥7 lesions	127 (0)	58 (1)	21 (9)	5 (15)	1 (16)	0 (16)

Figure 3

Progression-free survival and overall survival by number of metastatic lesions



Number at risk (number censored)	0	24	48	72	96	120
1 organ	293 (0)	89 (27)	46 (51)	18 (72)	6 (83)	3 (86)
2 organs	50 (0)	5 (7)	1 (7)	1 (7)	1 (7)	0 (8)
3 organs	5 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
≥4 organs	3 (0)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)

Number at risk (number censored)	0	24	48	72	96	120
1 organ	293 (0)	195 (22)	100 (63)	38 (101)	16 (116)	3 (124)
2 organs	50 (0)	20 (3)	1 (7)	1 (7)	1 (7)	0 (8)
3 organs	5 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
≥4 organs	3 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Figure 4

Progression-free survival and overall survival by number of organ involvement

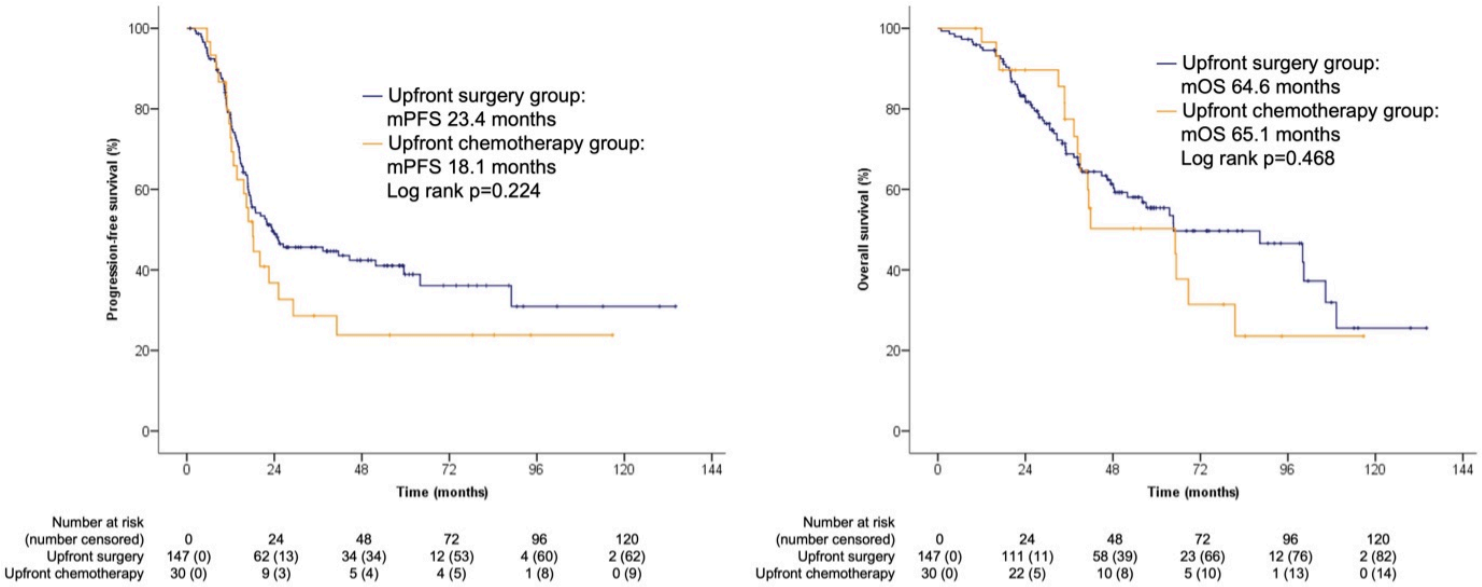


Figure 5

Progression-free survival and overall survival by therapeutic sequence in the low metastatic burden group

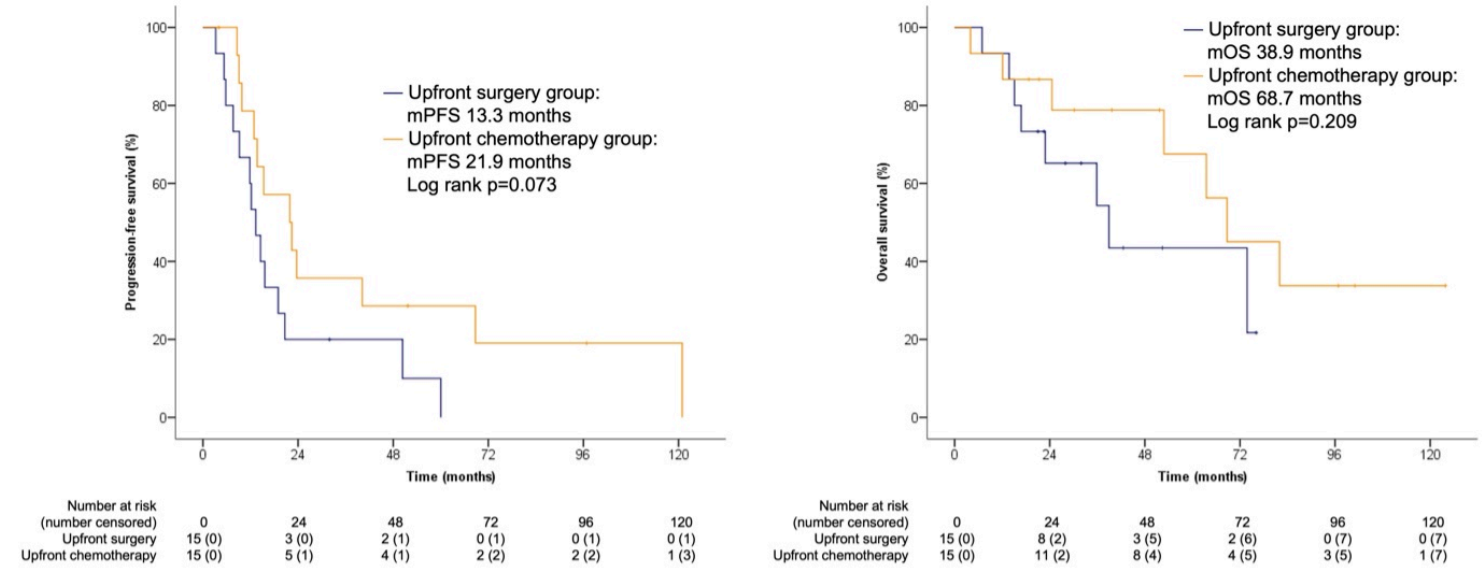


Figure 6

Progression-free survival and overall survival by therapeutic sequence in the intermediate metastatic burden group

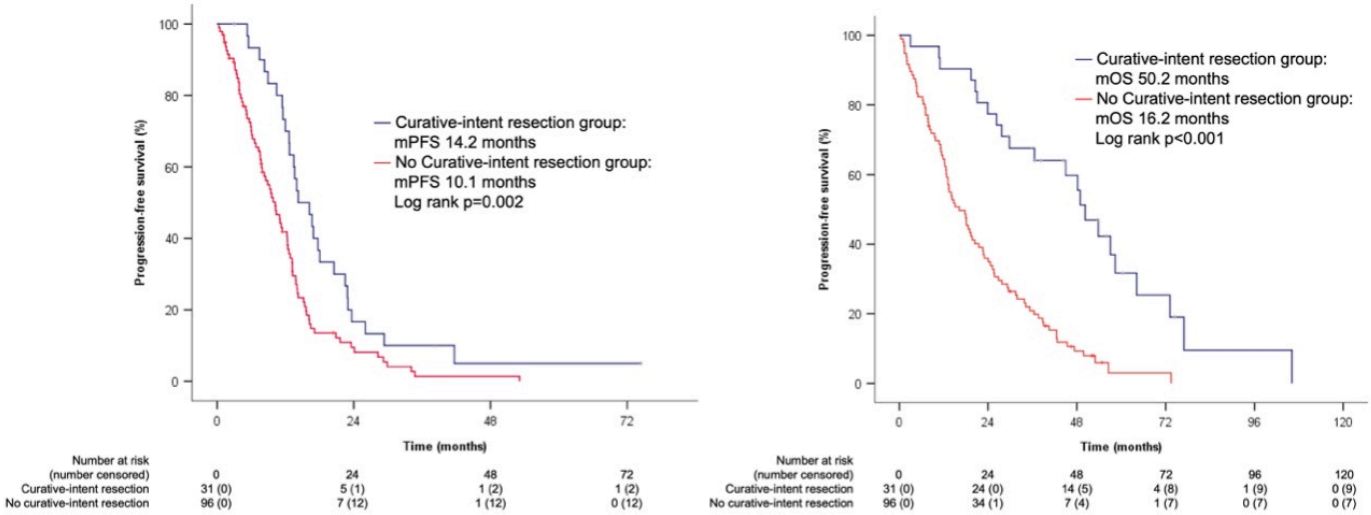


Figure 7

Progression-free survival and overall survival by curative-intent resection in the high metastatic burden group