Am J Cancer Res 2026;16(4):1354-1366
www.ajcr.us /ISSN:2156-6976/ajcr0172067

Original Article

Conversion-intent definitive liver-directed therapy improves survival in liver-predominant metastatic colorectal cancer

Ching-Cheng Chang[4,6], Yi-Hsin Liang[1,3,4,7], Been-Ren Lin[5,7], Chi-Hung Wu[8,9], Kuo-Hsing Chen[1,4,7], Chia-Yu Yeh[4], Kun-Huei Yeh[1,2,4,7]

[1]Graduate Institute of Oncology, College of Medicine, National Taiwan University, Taipei, Taiwan; [2]Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan; [3]Centers of Genomic and Precision Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan; [4]Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan; [5]Division of Colorectal Surgery in Department of Surgery, National Taiwan University Hospital, Taipei, Taiwan; [6]Department of Oncology, National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu, Taiwan; [7]National Taiwan University Cancer Center, Taipei, Taiwan; [8]Department of Medical Imaging, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan; [9]Department of Radiology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

Received February 11, 2026; Accepted April 9, 2026; Epub April 15, 2026; Published April 30, 2026

Abstract: Systemic therapy provides substantial disease control in metastatic colorectal cancer (mCRC), yet liver metastases often determine prognosis; real-world evidence for using conversion-intent definitive liver-directed therapy (DLDT) as consolidation after first-line treatment remains limited. We retrospectively analyzed 172 patients with initially unresectable, liver-predominant mCRC treated with first-line systemic therapy at National Taiwan University Hospital (2017-2023), comparing those who underwent conversion-intent DLDT during first-line treatment (n=100) with those who continued systemic therapy alone (n=72). Primary endpoints were time to treatment failure (TTF) and overall survival (OS). Conversion-intent DLDT markedly prolonged TTF (29.7 vs. 7.6 months; hazard ratio [HR] 0.16, P<0.001) and OS (47.0 vs. 17.7 months; HR 0.20, P<0.001). At 24 months, 49.6% of DLDT recipients remained on first-line therapy and 57.2% were alive, compared with 9.3% and 17.9% in controls. Outcomes were comparable between resection-based and ablation-only approaches. In multivariable models, conversion-intent DLDT remained independently associated with improved TTF (HR 0.16) and OS (HR 0.20), with similar associations observed across major molecular alterations. These findings support a multidisciplinary strategy incorporating conversion-intent DLDT after first-line systemic therapy for liver-predominant mCRC.

Keywords: Metastatic colorectal cancer, liver metastases, definitive liver-directed therapy, radiofrequency ablation, microwave ablation, *RAS* mutation

Introduction

Colorectal cancer (CRC) is the third most frequently diagnosed malignancy and the third leading cause of cancer-related death worldwide, including in Taiwan [1-5]. Liver metastasis significantly influences the disease trajectory and survival outcomes, as approximately 50% of patients develop liver metastases at some stage during their illness [6]. However, the optimal role and timing of definitive local treatment for liver-predominant disease after initial systemic therapy remain uncertain in routine clinical practice.

Currently, definitive liver-directed therapy (DLDT), including hepatectomy or image-guided thermal ablation with radiofrequency (RFA) or microwave (MWA), underpins modern multidisciplinary care [2, 7-12]. Surgical eligibility has broadened significantly; refinements in imaging, parenchymal-sparing techniques, and perioperative support have expanded resectability from <10% of patients in the 1980s to >50% presently, even for bilobar or multifocal disease [13]. If resection is not feasible because of limited future liver remnant, comorbidities, or proximity to critical structures, percutaneous ablation provides a minimally inva-

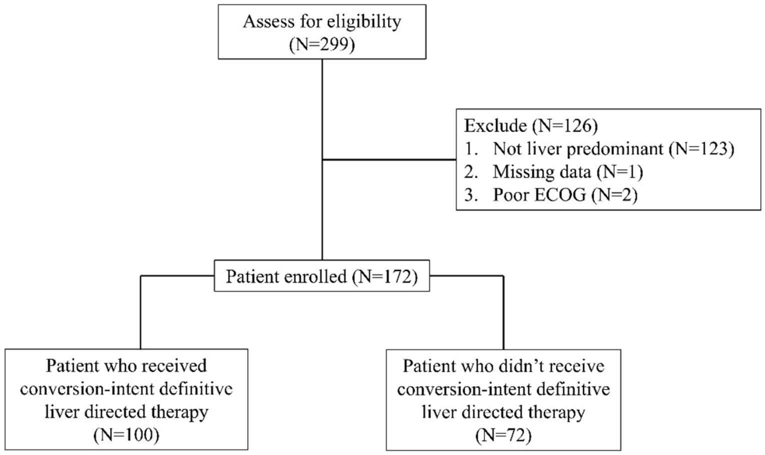

Figure 1. Study flowchart. Flowchart illustrating patient selection, inclusion and exclusion criteria, and final cohort allocation to conversion-intent DLDT and non- conversion-intent DLDT groups.

sive alternative. RFA coagulates tumors ≤3 cm via 350-500 MHz alternating current but is vulnerable to heat-sink effects near larger vessels <3 mm [14, 15] yielding pooled five-year overall survival (OS) of 30-40% [16-19]. In contrast, MWA (0.9-2.6 GHz) achieves higher temperatures, larger spherical zones (>6 cm), and faster ablations with reduced heat-sink susceptibility [20, 21]. Furthermore, modern 2.4 GHz systems can achieve durable local control approaching 98% at 4 years for subcentimeter lesions [22]. Other local modalities, such as irreversible electroporation, also exist, although hepatectomy and thermal ablation remain the dominant definitive approaches in routine practice [23-26]. Combined ablation-resection strategies further extend curative intent to patients with extensive bilobar disease while preserving functional parenchyma and maintaining oncologic efficacy [7-11].

Current evidence for DLDT in patients with metastatic colorectal cancer (mCRC) is mostly based on a small series of reports. Therefore, this single-institution retrospective study investigated the real-world impact of conversion-intent DLDT in patients with liver-predominant mCRC. By examining the clinical efficacy of DLDT across different molecular subgroups and treatment modalities, this study aimed to provide practical insights and inform future clinical decision-making regarding the management of liver-predominant mCRC.

Materials and methods

Patient enrollment

Clinical data of patients diagnosed with mCRC between 2017 and 2023 were retrieved from the Medical Information Management Office and Cancer Registry Office of the National Taiwan University Hospital (NTUH). The inclusion criteria were as follows; (1) presence of metastatic or recurrent CRC; (2) age ≥18 years; (3) complete medical records (including computed tomography and follow-up reports) at NTUH; (4) presence of initially unresectable liver-predominant metastases; and (5) receiving systemic therapy as the first-line treatment.

Patients were excluded if they (1) had a diagnosis of ≥2 active primary malignancies, (2) had an uncertain *RAS/BRAF*-mutation status, (3) did not have liver-predominant mCRC, or (4) had pathological diagnoses other than adenocarcinoma (squamous cell carcinoma or neuroendocrine carcinoma).

Liver-predominant metastatic disease was defined as either liver-only metastasis or liver-dominant metastatic disease in which more than 80% of all metastatic lesions, based on lesion counts on baseline staging imaging, were located in the liver, regardless of whether the primary colorectal tumor had been resected previously. According to the definition listed above, limited extrahepatic disease was allowed when deemed clinically controlled and technically compatible with a conversion-intent strategy; in practice, this generally referred to fewer than three extrahepatic metastatic lesions. Patient enrollment is summarized in **Figure 1**. This study was approved by the Institutional Review Board of NTUH (NTUH IRB: 202108112RINC).

Data collection

The following clinical and pathological data were extracted from medical records: (1) age at metastasis diagnosis, (2) sex, (3) pathology reports for *RAS/BRAF* and mismatch repair (MMR) status, (4) location of the primary CRC at initial diagnosis, (5) initial clinical stage, (6) metastatic sites, (7) modality of local therapy for liver metastasis, (8) regimen of first-line systemic treatment, (9) date of metastatic or recurrent CRC diagnosis, (10) date of first dose of first-line systemic treatment, (11) date of first dose of second-line systemic treatment, and (12) date of death or last follow-up before April 20, 2025.

Patients aged ≥65 years were classified as elderly patients. Right-sided colon cancer was defined as originating in the cecum, ascending colon, hepatic flexure, or transverse colon, whereas left-sided colon cancer included all other segments and the rectum. DLDT modalities included hepatectomy, liver ablation, or both. Liver ablation included RFA and MWA. A doublet regimen was defined as 5-FU in combination with irinotecan or oxaliplatin (FOLFOX or FOLFIRI). The triplet regimen was defined as a combination of irinotecan, oxaliplatin, leucovorin, and 5-FU (FOLFOXIRI). Triple wild-type (WT) was defined as wild-type extended *RAS* and *BRAF* with proficient mismatch repair (pMMR).

Conversion-intent DLDT was defined as hepatic resection, thermal ablation (radiofrequency ablation or microwave ablation), or a combination of both, performed after great responses from first-line systemic therapy with the intent to eradicate all radiographically visible liver metastases. All hepatic resections included in the DLDT group achieved microscopically margin-negative (R0) resection. In ablation cases, complete ablation was defined by post-procedural imaging showing no residual contrast enhancement in the treated lesion, and treatment planning followed contemporary principles aimed at achieving an adequate ablative margin, typically at least 5 mm and ideally larger when technically feasible. In routine practice, candidacy for conversion-intent DLDT was determined through multidisciplinary discussion involving medical oncology, hepatobiliary surgery, and interventional radiology. Selection was based on overall responses after first-line therapy, technical feasibility of complete local treatment, liver reserve, performance status, comorbidities, and the extent of extrahepatic disease.

Patients were categorized into DLDT and non-DLDT groups according to whether conversion-intent DLDT was performed after initiation of first-line systemic therapy.

Statistical analysis

OS was calculated from the date of metastatic or recurrent CRC diagnosis to the date of death or last follow-up before April 20, 2025. Time to treatment failure (TTF) was defined as the interval between initiation and discontinuation of first-line systemic therapy or last follow-up before April 20, 2025. Clinicopathological variables were compared using the chi-square test or Fisher's exact test, as appropriate. The Kaplan-Meier method was used to estimate survival probabilities and the corresponding 95% confidence intervals (CIs). Multivariate analyses were performed using the Cox proportional hazards model to identify factors associated with TTF and OS, with hazard ratios (HRs) and 95% CIs. Because DLDT was delivered after initiation of first-line systemic therapy, additional sensitivity analyses were performed to address potential immortal time bias. DLDT was modeled as a time-dependent covariate in Cox regression analyses for TTF and OS. In addition, a landmark analysis was performed using the median time from initiation of first-line systemic therapy to DLDT as the landmark time point. The landmark time was set at 4.86 months, corresponding to the median time from initiation of first-line systemic therapy to DLDT among patients who underwent DLDT. All statistical tests were two-sided, with a significance level of $P<0.05$. Statistical analyses were conducted using SPSS version 20.0 (IBM Corp., Chicago, IL, USA) and R version 4.5.0.

Ethical and humane considerations

This study was approved by the Institutional Review Board of National Taiwan University Hospital (NTUH IRB: 202108112RINC) and conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived because this was a retrospective analysis of fully de-identified data.

Results

Patient clinicopathological factors

A total of 172 patients with liver-predominant mCRC were included, with 100 (58.1%) receiv-

Table 1. Patient clinical characteristics

Characteristic	All patients (%)[a]	Definitive liver-directed treatment		P-value
		Y (%)[a]	N (%)[a]	
All	172 (100%)	100 (58.1%)[b]	72 (41.9%)[b]	
Gender				0.168
Female	80 (46.5%)	42 (42.0%)	38 (52.8%)	
Male	92 (53.5%)	58 (58.0%)	34 (47.2%)	
Age (years)				
Mean ± SD	59.9 ± 12.6	61.0 ± 12.6	58.5 ± 12.4	0.209
Age ≤65 years	126 (73.3%)	74 (74%)	52 (72.2%)	
Age >65 years	46 (26.7%)	26 (26%)	20 (27.8%)	
Primary site				0.489
Right-sided[c]	47 (27.3%)	25 (24%)	22 (30.6%)	
Left-sided[d]	125 (72.7%)	75 (75%)	50 (69.4%)	
Stage IV status				0.001[g]
De novo	141 (82.0%)	74 (74%)	67 (93.1%)	
Recurrent	31 (18.0%)	26 (26%)	5 (6.9%)	
Mutation Status				0.929
Wild type[e]	87 (50.6%)	51 (51%)	36 (50%)	
RAS mutant	75 (43.6%)	44 (44%)	31 (43.0%)	
BRAF V600E mutant	8 (4.7%)	4 (4%)	4 (5.6%)	
dMMR[f]	3 (1.7%)	2 (2%)	1 (1.4%)	
Biological agent use				0.138
No	15 (8.7%)	12 (12%)	3 (4.2%)	
Bevacizumab	85 (49.4%)	45 (45%)	40 (55.6%)	
Anti-EGFR monoclonal antibody	72 (41.9%)	43 (43%)	29 (40.3%)	
Fluoropyrimidine				1.000
No	4 (2.3%)	2 (2%)	2 (2.8%)	
Yes	168 (97.7%)	98 (98%)	70 (97.2%)	
Oxaliplatin- or Irinotecan-based regimen				0.708
Irinotecan	133 (77.3%)	78 (78%)	55 (76.4%)	
Oxaliplatin	30 (17.4%)	16 (16%)	14 (19.4%)	
Neither agent	5 (2.9%)	4 (4%)	1 (1.4%)	
Both	4 (2.3%)	2 (2%)	2 (2.8%)	

[a]The percentage was based on subgroup analysis. [b]The percentage was based on all 172 cases. [c]Includes the cecum, ascending colon, and transverse colon. [d]Including the splenic flexure, descending colon, sigmoid colon, and rectum. [e]*RAS* wild type, *BRAF* wild type, and preserved MMR. [f]One patient with *BRAF* V600E is dMMR. [g]$P<0.05$.

ing DLDT and the remaining 72 (41.9%) receiving systemic therapy alone as first-line treatment (**Figure 1**). The cohort was balanced with respect to sex with a median age of approximately 60 years. Tumors predominantly originated in the left colon or rectum, and the majority (approximately 80%) presented with de novo stage IV disease rather than recurrent metastases after previous curative resection (**Table 1**). Regarding molecular profiles, 50.6% of the patients had tumors that were triple WT for *RAS*, *BRAF*, and MMR, whereas the rest harbored either *RAS* mutations (43.6%), *BRAF* V600E mutations (4.7%), or deficient MMR (1.7%). Virtually all patients (98%) received combination chemotherapy with fluoropyrimidine plus oxaliplatin and/or irinotecan, and 91.3% received a biological agent as part of the first-line treatment (49.4% bevacizumab and 41.9% an anti-EGFR antibody). All patients were Asian. Importantly, there were no significant differences between the DLDT and non-DLDT groups in baseline demographic or clinical factors, including age, sex, primary tumor

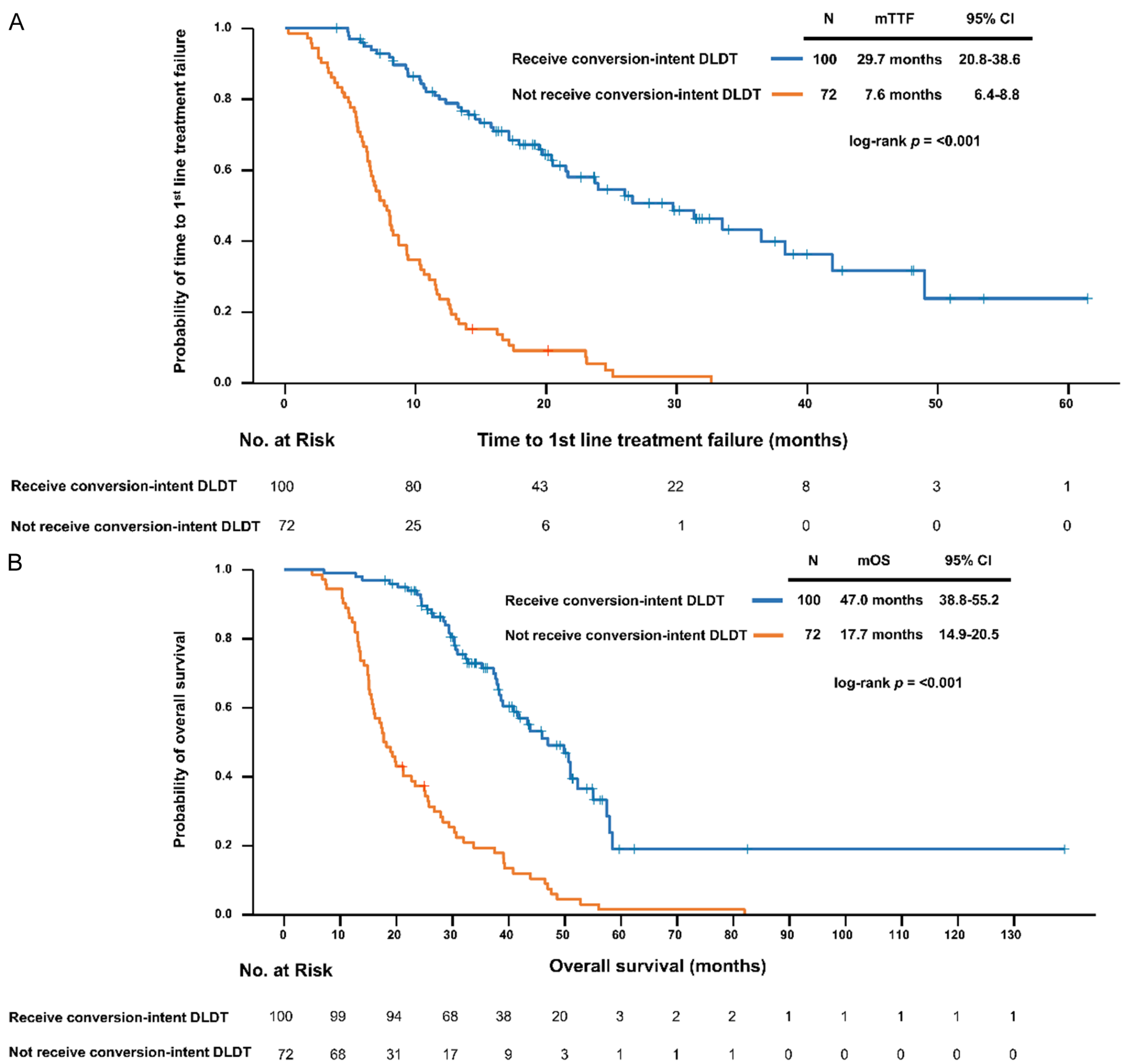

Figure 2. Kaplan-Meier analysis of treatment durability and overall survival according to conversion-intent definitive liver-directed therapy (DLDT). A: Time to treatment failure (TTF) from initiation of first-line systemic therapy. B: Overall survival (OS) from diagnosis of metastatic or recurrent colorectal cancer.

location, mutation status, and first-line chemotherapy regimen, except for a higher proportion of recurrent (rather than de novo) metastatic cases in the DLDT group. Patients with initially stage I-III disease were more likely to undergo DLDT than those with initially stage IV disease.

Survival outcomes

Patients who underwent conversion-intent DLDT experienced significantly prolonged first-line treatment. The median TTF in the DLDT and non-DLDT groups was 29.7 (95% CI: 20.8-38.6) and 7.6 (95% CI: 6.4-8.8) months, respectively (P<0.001) (**Figure 2A**). At one year, approximately 80% of patients in the DLDT group were still receiving the first-line regimen, whereas most non-DLDT patients experienced treatment discontinuation or progression. The Kaplan-Meier curves for TTF showed an early and sustained separation between the groups, with approximately 50% of DLDT patients still free of first-line treatment failure at two years, in contrast to <10% of those without DLDT. DLDT was associated with a substantially improved OS (median OS: 47.0 months [95% CI: 38.8-55.2] vs. 17.7 months [95% CI: 14.9-20.5], P<0.001) (**Figure 2B**). By three years after diagnosis, >50% of the DLDT group remained alive compared to <20% in the non-

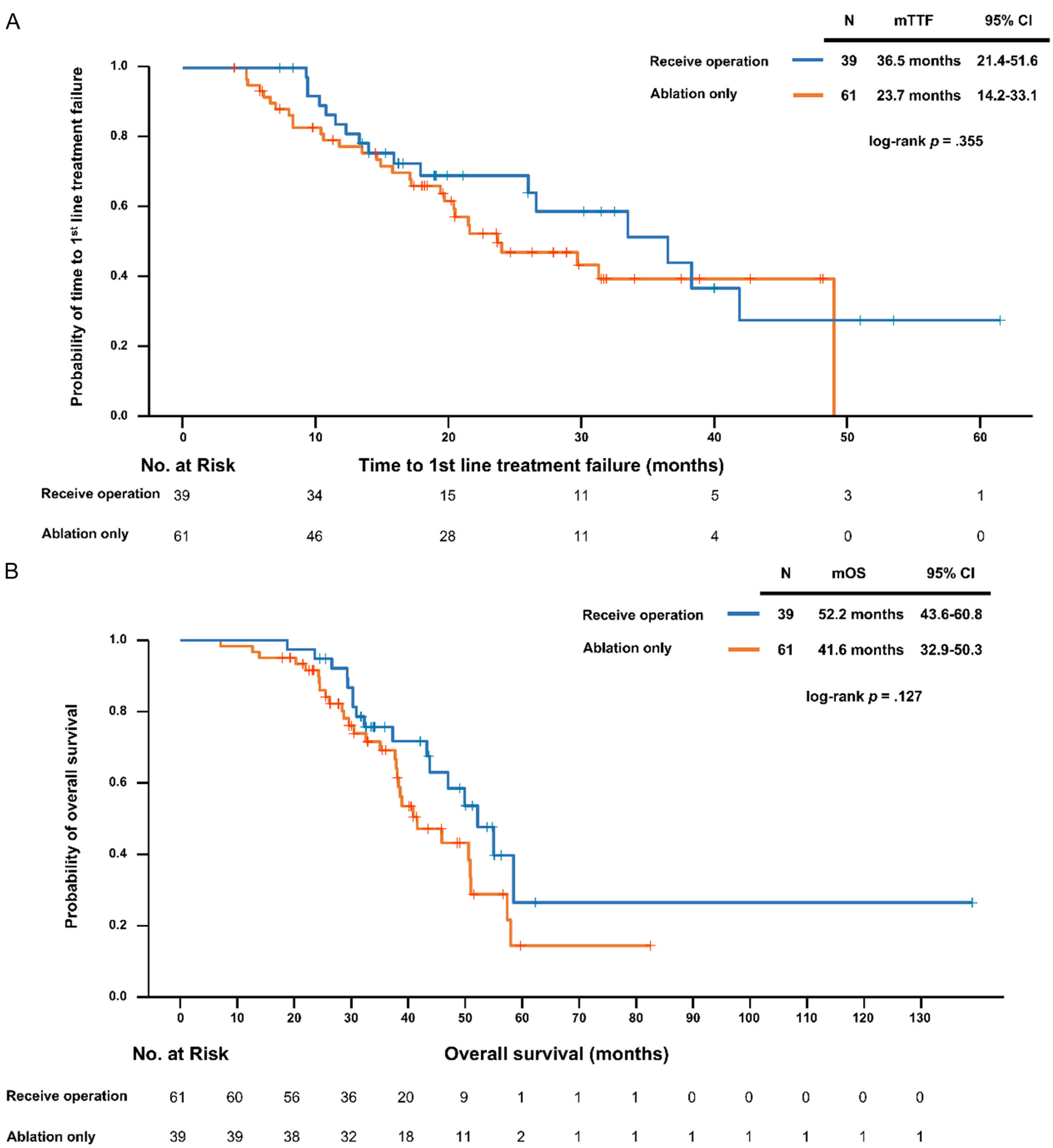

Figure 3. Comparison of outcomes between surgical resection and ablation-only approaches among patients receiving conversion-intent DLDT. A: TTF. B: OS stratified by hepatic resection (with or without ablation) versus ablation-only therapy.

DLDT group. The survival benefit of DLDT was observed across a spectrum of patients, highlighting the substantial impact of achieving local control of liver metastases.

Among the 100 patients with DLDT, 39 underwent hepatic resection (with or without ablation therapy) and 61 received ablation therapy only (RFA or MWA). There were no significant differences in the outcomes between the surgical and ablation approaches. Median TTF was 36.5 (95% CI: 21.4-51.6) and 23.7 (95% CI: 14.2-33.1) months in the surgery and ablation-only groups, respectively (**Figure 3A**, P=0.355). Median OS was numerically higher in the resection group (52.2 months, 95% CI: 43.6-60.8) compared to the ablation-only group (41.6 months, 95% CI: 32.9-50.3), without reaching statistical significance (**Figure 3B**, P=0.127). Both approaches to DLDT yielded

Table 2. Cox proportional hazards analysis for time to treatment failure (TTF) and overall survival (OS)

Variable	TTF			OS		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age						
≤65 years	1.00			1.00		
>65 years	0.736	0.490-1.104	0.138	1.082	0.723-1.620	0.701
Gender						
Female	1.00			1.00		
Male	0.978	0.660-1.449	0.913	1.197	0.807-1.776	0.372
Conversion-intent DLDT						
No	1.00			1.00		
Yes	0.156	0.101-0.241	<0.001[a]	0.197	0.130-0.297	<0.001[a]
Primary site						
Right-sided[b]	1.00			1.00		
Left-sided[c]	0.872	0.533-1.425	0.584	0.891	0.559-1.420	0.627
Stage IV status						
De novo	1.00			1.00		
Recurrent	0.683	0.396-1.179	0.171	0.580	0.336-0.999	0.049[a]
RAS/BRAF/MMR						
Triple WT[d]	1.00			1.00		
Non-WT	1.719	1.114-2.654	0.014[a]	2.044	1.328-3.146	0.001[a]
Oxaliplatin- or Irinotecan-based regimen						
Irinotecan	1.00			1.00		
Oxaliplatin	1.020	0.618-1.685	0.937	1.448	0.872-2.405	0.153

HR, hazard ratio. [a]*P*<0.05. [b]Including the cecum, ascending colon, and transverse colon. [c]Includes the splenic flexure, descending colon, sigmoid colon, and rectum. [d]Triple WT was defined as RAS wild-type, BRAF wild-type, and proficient MMR.

favorable long-term survival compared with non-DLDT.

Among the 100 patients who underwent DLDT, the median time from initiation of first-line systemic therapy to DLDT was 4.86 months (Interquartile Range: 3.22-8.91). In sensitivity analyses addressing immortal time bias, DLDT remained significantly associated with improved OS. In the time-dependent Cox model, DLDT was associated with improved OS (HR: 0.245, 95% CI: 0.167-0.358; P<0.001), which remained significant after adjustment (adjusted HR: 0.232, 95% CI: 0.155-0.347; P<0.001). Similarly, in the landmark analysis using 4.86 months as the landmark time, DLDT remained associated with significantly improved OS (HR: 0.426, 95% CI: 0.265-0.684; P< 0.001; adjusted HR: 0.429, 95% CI: 0.260-0.707; P<0.001).

Subgroup analyses

In multivariable Cox proportional-hazards analysis (**Table 2**), DLDT remained as an independent predictor of prolonged TTF (adjusted HR: 0.16; 95% CI: 0.10-0.24) and improved OS (HR: 0.20; 95% CI: 0.13-0.30). In contrast, *RAS/BRAF* mutation or dMMR status (HR: 2.04; 95% CI: 1.33-3.15, *P*=0.001) was associated with worse survival, whereas recurrent metastatic disease at presentation (HR: 0.58; 95% CI: 0.34-1.00, *P*=0.049) independently predicted longer survival. These factors further support the role of genetic and clinical characteristics in influencing the effectiveness of the DLDT in liver-predominant mCRC.

Patients with triple WT tumors (n=85) demonstrated superior outcomes compared with those with non-WT tumors (n=87). Kaplan-Meier analysis showed a significantly longer median TTF in the triple WT cohort than in the non-WT cohort (17.9 vs. 11.6 months, log-rank *P*= 0.049, **Figure 4A**). The median OS likewise favored WT patients (38.6 months) over the non-WT group (28.4 months, *P*=0.039, **Figure 4B**). Notably, the non-WT category included a small number of *BRAF* V600E (n=8) and mis-

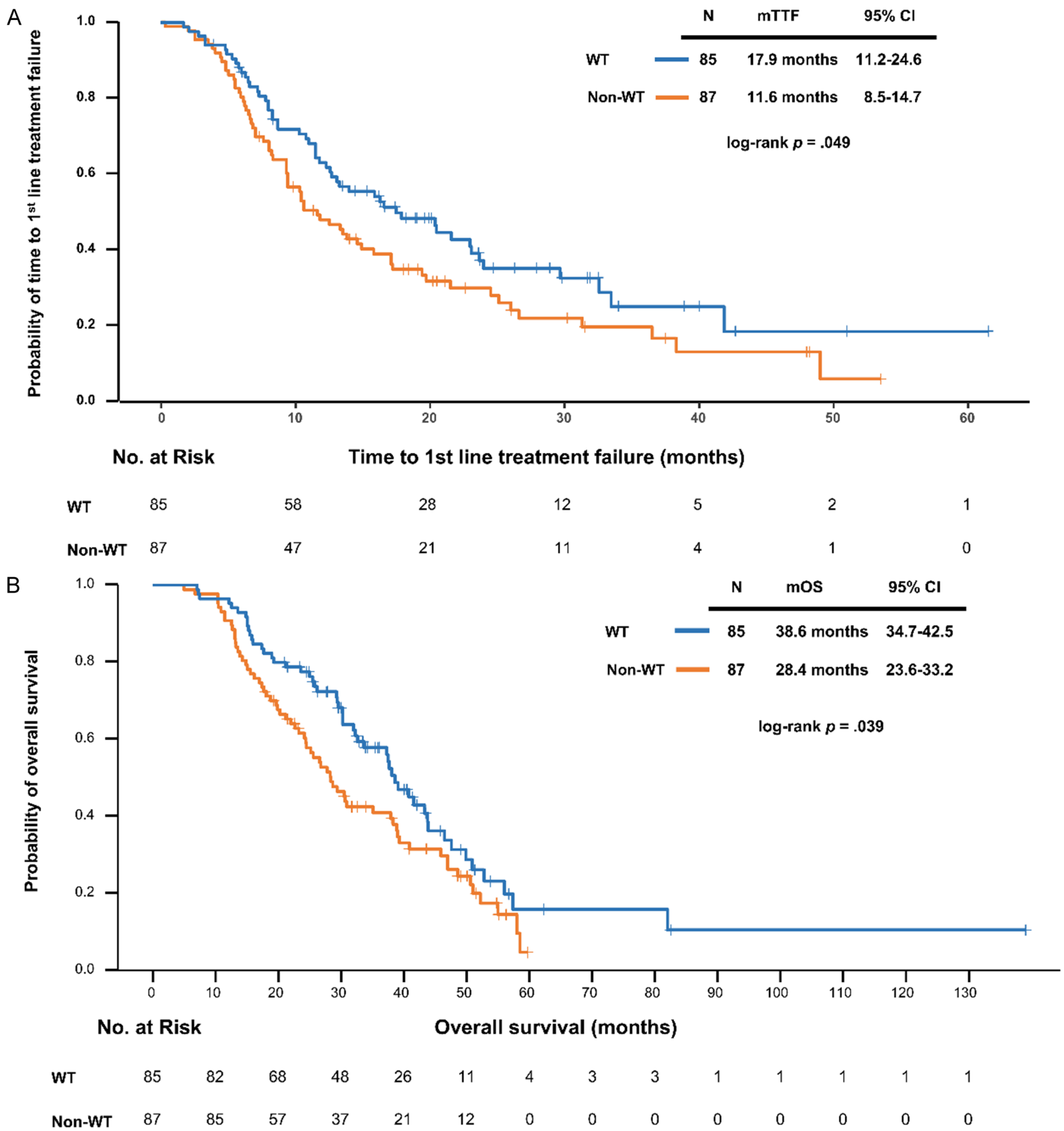

Figure 4. Survival outcomes according to tumor molecular status. A: TTF. B: OS stratified by triple wild-type (RAS/BRAF wild-type and proficient mismatch repair) versus non-WT tumors.

match repair-deficient (dMMR) cases (n=3). In multivariable Cox modeling, the presence of any mutation remained independently associated with poorer outcomes, with an adjusted HR of 1.72 (95% CI: 1.11-2.65, *P*=0.014) for TTF and 2.04 (95% CI: 1.33-3.15, *P*=0.001) for OS, relative to triple WT disease.

The association between DLDT and improved outcomes was observed in both the triple-WT and pooled non-WT subgroups. However, because BRAF V600E-mutant and dMMR cases were few, these subgroup analyses should be considered exploratory. Among WT patients, those who underwent DLDT had significantly prolonged median TTF (33.5 vs. 8.3 months) and OS (49.9 vs. 21.2 months, both *P*<0.001) compared to those in the non-DLDT group. Similarly, in the non-WT subgroup, patients receiving DLDT achieved substantially longer median TTF (26.0 vs. 6.5 months) and OS (47.0 vs. 16.2 months; both *P*<0.001, **Figure 5**).

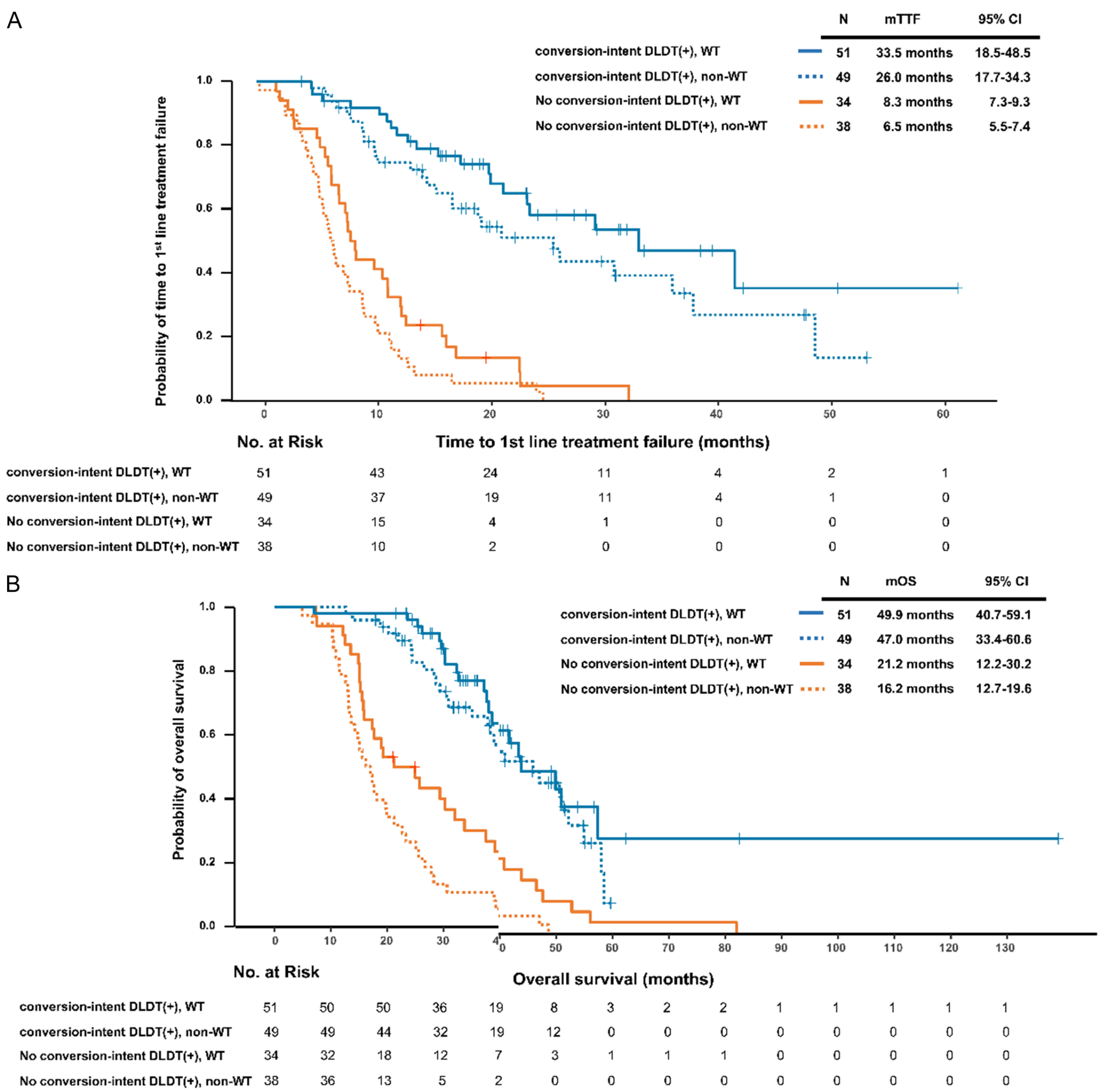

Figure 5. Effect of conversion-intent definitive liver-directed therapy across molecular subgroups. A: TTF. B: OS according to DLDT status in patients with triple wild-type tumors and non-WT tumors.

Statistical testing revealed no significant interaction detected between molecular subgroup and the association of DLDT with survival.

Discussion

Our study provides real-world evidence supporting the efficacy of conversion-intent DLDT, including hepatic resection and thermal ablation, in patients with liver-predominant mCRC. Among 100 DLDT-treated patients, median TTF was quadrupled (29.7 vs. 7.6 months) and median OS was nearly tripled (47.0 vs. 17.7 months) relative to matched non-DLDT controls (P<0.001). Resection (± ablation) and ablation alone achieved comparable OS (52.2 vs. 41.6 months, P=0.13), supporting the clinical relevance of modern ablative techniques as a definitive local option in selected patients. Crucially, the association between DLDT and improved outcomes was observed in both major molecular strata, although less common subgroups should be interpreted cautiously because of limited sample size.

These findings echo large series and meta-analyses of colorectal liver metastases (CRLM), in which five-year OS after aggressive local treatment ranges from 25-69% and median OS frequently exceeds 40-50 months [27-29].

The 47.0-month median OS observed in the current study's DLDT group aligns well within this established range for aggressive local treatment, strongly resonating with previous literature that demonstrates the survival advantage of aggressive local management for liver-predominant metastatic disease. Direct comparative studies have underscored the substantial survival advantage of DLDT over systemic therapy alone in liver-predominant mCRC. A large multi-institutional database analysis highlighted stark differences in five-year OS (47.8% for hepatectomy alone, 35.9% for combined hepatectomy plus RFA, and 29.2% for RFA alone) compared with only 7.4% for non-aggressive treatment (systemic therapy/supportive care). Multivariable analysis from that study yielded HRs strongly favoring DLDT (HR 0.22 for hepatectomy and 0.29 for RFA) [29]. Similarly, a case-matched study comparing resection to systemic therapy demonstrated a significantly longer median OS with resection (56 vs. 26.5 months, *P*=0.027) [30]. These findings are in good agreement with our results.

Our findings support the survival benefit of DLDT, consistent with previous randomized trials (EORTC 40004/CLOCC) [31] and observational studies [32] demonstrating prolonged survival outcomes with hepatic resection and thermal ablation compared with systemic therapy alone. Although resection (often combined with ablation) showed a numerically longer median OS than ablation alone in our cohort (52.2 vs. 41.6 months), the difference was not statistically significant, further supported by the findings from the COLLISION trial [11] which showed non-inferior survival for ablation versus resection for lesions ≤3 cm (HR: 1.05). Systematic reviews consistently report superior local control with resection, but the advantages, such as lower morbidity, minimal invasiveness, reduced blood loss, shorter hospital stays, and repeatability, make it particularly attractive in patients with smaller lesions, challenging tumor locations, or significant comorbidities [32, 33]. Selection bias favoring healthier patients with better anatomy for surgical resection likely accounts for the superior outcomes historically attributed to resection [32]. Evidence suggests that if comparisons are restricted to specific patient subgroups, particularly those with smaller tumors (≤2 cm or ≤3 cm in diameter), the survival outcomes between resection and ablation may become comparable [32]. Thus, therapeutic decisions should balance the goals of achieving durable local control via surgery against the practical benefits of minimally invasive ablation, particularly in anatomically challenging or high-risk patients.

The negative prognostic impact of activating *RAS* mutations and *BRAF* V600E observed in our study aligns with the historical data. Prognostically adverse mutations in *KRAS/NRAS* (40-50%) and *BRAF* V600E (8-12%) shorten survival even after DLDT; however [34-36] our data and previous series demonstrate that these patients still derive a relative benefit from local therapy compared to systemic treatment alone [37-40]. Molecular status influences overall survival outcomes and therapeutic sequencing decisions. For instance, a recent large-scale Taiwanese study demonstrated that first-line anti-EGFR therapy in *KRAS* WT patients significantly improved OS and increased conversion-intent resection or RFA rates compared with bevacizumab-based therapies (29.6% vs. 22.6%), shortening the median time to conversion (5.7 vs. 7.1 months) [5]. These findings emphasize the distinction between overall survival, inherently lower in *RAS/BRAF* mutant patients, and relative benefit, which remains meaningful across molecular subgroups. Thus, molecular profiling should inform therapeutic sequencing, particularly the strategic early use of anti-EGFR antibodies in patients with *RAS* WT and left-sided mCRC to maximize the conversion potential without categorically precluding DLDT when technically feasible and clinically appropriate.

This study provides valuable real-world data on the effect of DLDT on liver-predominant mCRC. However, there are several limitations. First, its retrospective single-center design is inherently subject to selection bias and residual confounding. Patients selected for DLDT may have had more favorable disease control or technical suitability for local therapy than those who continued systemic therapy alone. We were also unable to comprehensively adjust for several liver tumor burden variables, including lesion number, bilobar distribution, and maximal tumor size, which are clinically relevant determinants of both DLDT eligibility and prognosis. Second, because DLDT was delivered after initiation of first-line systemic therapy, immortal time bias cannot be fully excluded, although additional time-dependent and landmark analyses were performed to address this concern. Third, several molecularly defined subgroups, especially BRAF *V600E*-mutant and dMMR tumors, were small and therefore unsuitable for definitive subgroup inference. Furthermore, detailed procedural characteristics of ablation (RFA vs. MWA) and precise tumor characteristics (exact number and size distribution of metastases treated per patient, proximity to vessels) hinder a more nuanced interpretation and comparison of outcomes, especially between DLDT modalities. Finally, the study was conducted at a single tertiary referral center in an all-Asian population, which may limit generalizability of the findings to broader clinical practice settings. These limitations underline the need for caution in interpreting the magnitude of the DLDT effect as solely treatment-related, and highlight the need for prospective validation.

In conclusion, in this retrospective real-world cohort, conversion-intent DLDT was strongly associated with prolonged TTF and OS in selected patients with liver-predominant mCRC. Our findings support considering DLDT as a part of multimodality treatment strategies, advocating its consideration in multidisciplinary team evaluations to optimize patient outcomes.

Acknowledgements

We thank all the patients and their families for their support in this study and also thank the Medical Information Management Office and the Cancer Registry Office of NTUH for facilitating access to institutional datasets. This study was supported by the Ministry of Health and Welfare of Taiwan (grant number: MOHW113-TDU-B-221-134010).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Kun-Huei Yeh, Department of Oncology, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 10002, Taiwan. Tel: +886-223123456 Ext. 266285; Fax: +886-223711174; E-mail: khyeh@ntu.edu.tw

References

[1] Liang YH, Shao YY, Chen HM, Cheng AL, Lai MS and Yeh KH. Irinotecan and oxaliplatin might provide equal benefit as adjuvant chemotherapy for patients with resectable synchronous colon cancer and liver-confined metastases: a nationwide database study. Anticancer Res 2017; 37: 7095-7104.

[2] Cervantes A, Adam R, Roselló S, Arnold D, Normanno N, Taïeb J, Seligmann J, De Baere T, Osterlund P, Yoshino T and Martinelli E; ESMO Guidelines Committee. Metastatic colorectal cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol 2023; 34: 10-32.

[3] Siegel RL, Giaquinto AN and Jemal A. Cancer statistics, 2024. CA Cancer J Clin 2024; 74: 12-49.

[4] TC R. http://tcr.cph.ntu.edu.tw/main.php?Page=N1. Taiwan Cancer Registry. 2019.

[5] Liang YH, Chen KH and Shao YY. Treatment outcome comparisons of first-line targeted therapy in patients with KRAS wild-type metastatic colorectal cancer: a nationwide database study. Cancer Med 2023; 12: 15176-15186.

[6] Donadon M, Ribero D, Morris-Stiff G, Abdalla EK and Vauthey JN. New paradigm in the management of liver-only metastases from colorectal cancer. Gastrointest Cancer Res 2007; 1: 20-27.

[7] Creasy JM, Sadot E, Koerkamp BG, Chou JF, Gonen M, Kemeny NE, Balachandran VP, Kingham TP, DeMatteo RP, Allen PJ, Blumgart LH, Jarnagin WR and D'Angelica MI. Actual 10-year survival after hepatic resection of colorectal liver metastases: what factors preclude cure? Surgery 2018; 163: 1238-1244.

[8] van Amerongen MJ, Jenniskens SFM, van den Boezem PB, Fütterer JJ and de Wilt JHW. Radiofrequency ablation compared to surgical resection for curative treatment of patients with colorectal liver metastases - a meta-analysis. HPB (Oxford) 2017; 19: 749-756.

[9] Karanicolas PJ, Jarnagin WR, Gonen M, Tuorto S, Allen PJ, DeMatteo RP, D'Angelica MI and Fong Y. Long-term outcomes following tumor ablation for treatment of bilateral colorectal liver metastases. JAMA Surg 2013; 148: 597-601.

[10] Meijerink MR, Puijk RS, van Tilborg AAJM, Henningsen KH, Fernandez LG, Neyt M, Heymans J, Frankema JS, de Jong KP, Richel DJ, Prevoo W and Vlayen J. Radiofrequency and microwave ablation compared to systemic chemotherapy and to partial hepatectomy in the treatment of colorectal liver metastases: a sys-

tematic review and meta-analysis. Cardiovasc Intervent Radiol 2018; 41: 1189-1204.
[11] van der Lei S, Puijk RS, Dijkstra M, Schulz HH, Vos DJW, De Vries JJJ, Scheffer HJ, Lissenberg-Witte BI, Aldrighetti L, Arntz M, Barentsz MW, Besselink MG, Bracke B, Bruijnen RCG, Buffart TE, Burgmans MC, Chapelle T, Coolsen MME, de Boer SW, de Cobelli F, de Jong K, de Wilt JHW, Diederik AL, Dooper AMC, Draaisma WA, Eker HH, Erdmann JI, Futterer JJ, Geboers B, Groot GMC, Hagendoorn J, Hartgrink HH, Horsthuis K, Hurks R, Jenniskens SFM, Kater M, Kazemier G, Kist JW, Klaase JM, Knapen RRMM, Kruimer JWH, Lamers ABGN, Leclercq WKG, Liefers GJ, Manusama ER, Meier MAJ, Melenhorst MCAM, Mieog JSD, Molenaar QI, Nielsen K, Nijkamp MW, Nieuwenhuijs VB, Nota IMGC, Op de Beeck B, Overduin CG, Patijn GA, Potters FH, Ratti F, Rietema FJ, Ruiter SJS, Schouten EAC, Schreurs WH, Serafino G, Sietses C, Slooter GD, Smits MLJ, Soykan EA, Spaargaren GJ, Stommel MWJ, Timmer FEF, van Baardewijk LJ, van Dam RM, van Delden OM, van den Bemd BAT, van den Bergh JE, van den Boezem PB, van der Leij C, van der Meer RW, van der Meijs BBM, van der Ploeg APT, van der Reijden JJ, van Duijvendijk P, van Erkel AR, van Geel AM, Van Heek NT, van Manen CJ, van Rijswijk CSP, van Waesberghe JHTM, Versteeg KS, Vink T, Zijlstra IAJ, Zonderhuis BM, Swijnenburg RJ, van den Tol MP and Meijerink MR. Thermal ablation versus surgical resection of small-size colorectal liver metastases (COLLISION): an international, randomised, controlled, phase 3 non-inferiority trial. Lancet Oncol 2025; 26: 187-199.
[12] Liang YH, Shao YY, Chen JY, Liang PC, Cheng AL and Lin ZZ. Modern prospection for hepatic arterial infusion chemotherapy in malignancies with liver metastases. Int J Hepatol 2013; 2013: 141590.
[13] Weber SM, Jarnagin WR, DeMatteo RP, Blumgart LH and Fong Y. Survival after resection of multiple hepatic colorectal metastases. Ann Surg Oncol 2000; 7: 643-650.
[14] Knavel EM and Brace CL. Tumor ablation: common modalities and general practices. Tech Vasc Interv Radiol 2013; 16: 192-200.
[15] Lu DS, Raman SS, Limanond P, Aziz D, Economou J, Busuttil R and Sayre J. Influence of large peritumoral vessels on outcome of radiofrequency ablation of liver tumors. J Vasc Interv Radiol 2003; 14: 1267-1274.
[16] Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, Lin XJ and Lau WY. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg 2006; 243: 321-328.
[17] Huang J, Yan L, Cheng Z, Wu H, Du L, Wang J, Xu Y and Zeng Y. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Ann Surg 2010; 252: 903-912.
[18] Feng K, Yan J, Li X, Xia F, Ma K, Wang S, Bie P and Dong J. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol 2012; 57: 794-802.
[19] Decadt B and Siriwardena AK. Radiofrequency ablation of liver tumours: systematic review. Lancet Oncol 2004; 5: 550-560.
[20] Liang P and Wang Y. Microwave ablation of hepatocellular carcinoma. Oncology 2007; 72 Suppl 1: 124-131.
[21] Ding J, Jing X, Liu J, Wang Y, Wang F, Wang Y and Du Z. Comparison of two different thermal techniques for the treatment of hepatocellular carcinoma. Eur J Radiol 2013; 82: 1379-1384.
[22] Leung U, Kuk D, D'Angelica MI, Kingham TP, Allen PJ, DeMatteo RP, Jarnagin WR and Fong Y. Long-term outcomes following microwave ablation for liver malignancies. Br J Surg 2015; 102: 85-91.
[23] Lee EW, Thai S and Kee ST. Irreversible electroporation: a novel image-guided cancer therapy. Gut Liver 2010; 4 Suppl 1: S99-S104.
[24] Faroja M, Ahmed M, Appelbaum L, Ben-David E, Moussa M, Sosna J, Nissenbaum I and Goldberg SN. Irreversible electroporation ablation: is all the damage nonthermal? Radiology 2013; 266: 462-470.
[25] Thomson KR, Cheung W, Ellis SJ, Federman D, Kavnoudias H, Loader-Oliver D, Roberts S, Evans P, Ball C and Haydon A. Investigation of the safety of irreversible electroporation in humans. J Vasc Interv Radiol 2011; 22: 611-621.
[26] Kingham TP, Karkar AM, D'Angelica MI, Allen PJ, Dematteo RP, Getrajdman GI, Sofocleous CT, Solomon SB, Jarnagin WR and Fong Y. Ablation of perivascular hepatic malignant tumors with irreversible electroporation. J Am Coll Surg 2012; 215: 379-387.
[27] Calderon Novoa F, Ardiles V, de Santibañes E, Pekolj J, Goransky J, Mazza O, Sánchez Claria R and de Santibañes M. Pushing the limits of surgical resection in colorectal liver metastasis: how far can we go? Cancers (Basel) 2023; 15: 2113.
[28] Morris EJ, Forman D, Thomas JD, Quirke P, Taylor EF, Fairley L, Cottier B and Poston G. Surgical management and outcomes of colorectal cancer liver metastases. Br J Surg 2010; 97: 1110-1118.
[29] Canseco LM, Liu YW, Lu CC, Lee KC, Chen HH, Hu WH, Tsai KL, Yang YH, Wang CC and Hung CH. Survival evidence of local control for

colorectal cancer liver metastases by hepatectomy and/or radiofrequency ablation. Cancers (Basel) 2023; 15: 4434.

[30] de Ridder JAM, van der Stok EP, Mekenkamp LJ, Wiering B, Koopman M, Punt CJA, Verhoef C and de Wilt JH. Management of liver metastases in colorectal cancer patients: a retrospective case-control study of systemic therapy versus liver resection. Eur J Cancer 2016; 59: 13-21.

[31] Ruers T, Punt C, Van Coevorden F, Pierie JPEN, Borel-Rinkes I, Ledermann JA, Poston G, Bechstein W, Lentz MA, Mauer M, Van Cutsem E, Lutz MP and Nordlinger B; EORTC Gastro-Intestinal Tract Cancer Group; Arbeitsgruppe Lebermetastasen und-tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO) and the National Cancer Research Institute Colorectal Clinical Study Group (NCRI CCSG). Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). Ann Oncol 2012; 23: 2619-2626.

[32] Todeschini L, Caimano M, Mattia A, Cristin L, Martinino A, Bianco G, Spoletini G and Giovinazzo F. Radiofrequency ablation versus surgical resection in colorectal liver metastasis: insight from an umbrella review. Front Oncol 2025; 15: 1494996.

[33] Abdalla EK, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR, Hess K and Curley SA. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 2004; 239: 818-825; discussion 825-817.

[34] Peeters M, Kafatos G, Taylor A, Gastanaga VM, Oliner KS, Hechmati G, Terwey JH and van Krieken JH. Prevalence of RAS mutations and individual variation patterns among patients with metastatic colorectal cancer: a pooled analysis of randomised controlled trials. Eur J Cancer 2015; 51: 1704-1713.

[35] Bylsma LC, Gillezeau C, Garawin TA, Kelsh MA, Fryzek JP, Sangaré L and Lowe KA. Prevalence of RAS and BRAF mutations in metastatic colorectal cancer patients by tumor sidedness: a systematic review and meta-analysis. Cancer Med 2020; 9: 1044-1057.

[36] Modest DP, Ricard I, Heinemann V, Hegewisch-Becker S, Schmiegel W, Porschen R, Stintzing S, Graeven U, Arnold D, von Weikersthal LF, Giessen-Jung C, Stahler A, Schmoll HJ, Jung A, Kirchner T, Tannapfel A and Reinacher-Schick A. Outcome according to KRAS-, NRAS- and BRAF-mutation as well as KRAS mutation variants: pooled analysis of five randomized trials in metastatic colorectal cancer by the AIO colorectal cancer study group. Ann Oncol 2016; 27: 1746-1753.

[37] Vauthey JN, Zimmitti G, Kopetz SE, Shindoh J, Chen SS, Andreou A, Curley SA, Aloia TA and Maru DM. RAS mutation status predicts survival and patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases. Ann Surg 2013; 258: 619-626; discussion 626-7.

[38] Schirripa M, Bergamo F, Cremolini C, Casagrande M, Lonardi S, Aprile G, Yang D, Marmorino F, Pasquini G, Sensi E, Lupi C, De Maglio G, Borrelli N, Pizzolitto S, Fasola G, Bertorelle R, Rugge M, Fontanini G, Zagonel V, Loupakis F and Falcone A. BRAF and RAS mutations as prognostic factors in metastatic colorectal cancer patients undergoing liver resection. Br J Cancer 2015; 112: 1921-1928.

[39] Wang PP, Lin C, Wang J, Margonis GA and Wu B. BRAF mutations in colorectal liver metastases: prognostic implications and potential therapeutic strategies. Cancers (Basel) 2022; 14: 4067.

[40] Brudvik KW, Kopetz SE, Li L, Conrad C, Aloia TA and Vauthey JN. Meta-analysis of KRAS mutations and survival after resection of colorectal liver metastases. Br J Surg 2015; 102: 1175-1183.