

Article

Conversion Strategy in Left-Sided RAS/BRAF Wild-Type Metastatic Colorectal Cancer Patients with Unresectable Liver-Limited Disease: A Multicenter Cohort Study

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Simple Summary: Around 70% of patients suffering from colorectal cancer (CRC) develop liver metastases. In the present multicentric cohort study, we explored the efficacy of a conversion strategy in a selected population of 272 left-sided RAS/BRAF wild-type CRC patients with liver-limited metastatic disease. The conversion rate was 24.1%. Fifty-six patients undergoing surgical resection after induction treatment had a significant survival advantage compared to those receiving systemic

treatment not leading to surgery. There was no difference in survival between ultimately resectable patients and those who had liver resection with perioperative systemic treatment. Our study confirms that in selected cases the combination of systemic treatment with surgical resection can remarkably improve survival outcomes.

Abstract: Colorectal cancer (CRC) patients frequently develop liver metastases. Different treatment strategies are available according to the timing of appearance, the burden of metastatic disease, and the performance status of the patient. Systemic treatment (ST) represents the cornerstone of metastatic disease management. However, in select cases, combined ST and surgical resection can lead to remarkable survival outcomes. In the present multicentric cohort study, we explored the efficacy of a conversion strategy in a selected population of left-sided RAS/BRAF wild-type CRC patients with liver-limited metastatic disease. **Methods:** The primary endpoint was to compare survival outcomes of patients undergoing ST not leading to surgery, liver resection after conversion ST, and hepatic resection with perioperative ST. Furthermore, we explored survival outcomes depending on whether the case was discussed within a multidisciplinary team. **Results:** Between 2012 and 2020, data from 690 patients respecting the inclusion criteria were collected. Among these, 272 patients were deemed eligible for the analysis. The conversion rate was 24.1% of cases. Fifty-six (20.6%) patients undergoing surgical resection after induction treatment (i.e., ultimately resectable) had a significant survival advantage compared to those receiving systemic treatment not leading to surgery (176 pts, 64.7%) (5-year OS 60.8% and 11.7%, respectively, Log Rank test $p < 0.001$; HR = 0.273; 95% CI: 0.16–0.46; $p < 0.001$; 5-year PFS 22.2% and 6.3%, respectively, Log Rank test $p < 0.001$; HR = 0.447; 95% CI: 0.32–0.63; $p < 0.001$). There was no difference in survival between ultimately resectable patients and those who had liver resection with perioperative systemic treatment (potentially resectable—40 pts) (5-year OS 71.1%, Log Rank test $p = 0.311$. HR = 0.671; 95% CI: 0.31–1.46; $p = 0.314$; 5-year PFS 25.7%, Log Rank test $p = 0.305$. HR = 0.782; 95% CI: 0.49–1.25; $p = 0.306$). **Conclusions:** In our selected population of left-sided RAS/BRAF wild-type colorectal cancer patients with liver-limited disease, a conversion strategy was confirmed to provide a survival benefit. Patients not deemed surgical candidates at the time of diagnosis and patients judged resectable with perioperative systemic treatment have similar survival outcomes.

Keywords: left colon cancer; rectal cancer; CRC; colorectal liver metastases; conversion therapy; liver resection; hepatectomy

1. Introduction

Fourteen to eighteen percent of patients suffering from colorectal cancer (CRC) present metastases at the time of diagnosis [1]. Approximately 70% of CRC patients experience metastatic disease to the liver [1,2]. According to major guidelines, the preferred option as first-line treatment for patients with unresectable left-sided RAS and BRAF wild-type metastatic colorectal cancer (mCRC) is represented by a cytotoxic fluoropyrimidine-based doublet (FOLFOX or FOLFIRI) in association with an Anti-epidermal growth factor receptor monoclonal antibody (i.e., EGFRi, cetuximab, or panitumumab) [3,4]. In this regard, a landmark retrospective pooled analysis of six randomized phase III trials showed a significant survival benefit for doublet plus EGFRi compared to doublet plus bevacizumab in RAS wild-type tumors originating from the left side of the colon, and this trend has been confirmed in real-life settings [5,6]. Although systemic treatment remains the cornerstone of metastatic disease management, with different emerging strategies after induction treatment in the never-resectable disease [7], surgical resection has progressively gained interest in the scientific community.

Treatment options include simultaneous resection of the primary tumor and liver in light of synchronous disease or a staged approach for both synchronous and metachronous diseases [8]. The latter encompasses upfront resection of the primary tumor or liver

resection followed by adjuvant systemic treatment (ST) before bowel resection or perioperative ST with liver resection followed by bowel resection. Unfortunately, only 10–20% of patients developing colorectal liver metastases (CRLM) are deemed eligible for liver resection, mainly due to heavy disease burden; however, promising results have been reported in terms of conversion rate after the administration of highly effective chemotherapy (CT) regimens with or without targeted agents [9–14].

Over the years, multiple guidelines and consensus have stratified CRLM patients based on clinical and biological characteristics of the tumor, technical resectability, and spread of the disease. While patients suffering from metastatic liver disease with good prognostic features (single and small lesions) are considered eligible for upfront surgical resection, patients with biologically more aggressive disease and/or presenting metastases adjacent to major vascular/biliary structures (borderline/potentially resectable) may benefit from perioperative ST. In case the spread of the disease hinders the possibility of surgical resection with curative intent, doublet or triplet ST regimens should be adopted to induce tumor shrinkage leading to surgical resection (initially unresectable/ultimately resectable patients) [15–18].

The aim of the present study is to retrospectively assess the efficacy of conversion therapy to prolong survival in a molecularly selected population of left-sided RAS/BRAF wild-type mCRC patients with liver-limited disease, according to the abovementioned classification and treated with doublet chemotherapy plus EGFRi.

2. Methods

2.1. Study Population

In the present multi-institutional study, data were retrospectively collected from patients diagnosed with liver metastases due to RAS/BRAF wild-type left-sided colon or rectal cancer and consecutively treated from March 2012 to October 2020.

2.2. Study Design

Demographics, clinicopathology, tumor biology, disease burden, treatment strategy, neoadjuvant treatments, surgical details, postoperative treatments, disease relapse, disease-related death, and follow-up information were gathered to build the dataset.

Baseline resectability of CRC liver metastases was assessed by surgeons, radiologists, and oncologists of each center, within or outside a defined multidisciplinary team (MDT), according to their local clinical practice. In case of baseline technical resectability (i.e., major hepatectomy, lobectomy, or other demolitive surgery not required), the decision to administer a preoperative treatment was related to the presence of biologically challenging criteria [19].

For convenience, the classification provided by Bittoni et al. and the Fong criteria were adopted [18,20]. Based on disease burden, patients were a posteriori classified as potentially resectable or unresectable.

Patients were defined as “potentially resectable” either when presenting biological challenges according to FONG criteria (multiple metastases, size >5 cm, positive lymph nodes at primary tumor, synchronous metastases or DFS <12 months, CEA >100 ng/mL, as assessed at baseline before beginning the systemic treatment) or technical challenges (tumor close to hepatic veins or portal branches, major hepatectomy required). These patients were considered eligible for perioperative chemotherapy and subsequent surgical resection.

On the other hand, patients judged as unresectable have been further classified as ultimately resectable (>70–80% of liver involvement, <25% remnant after resection, and six segments involved) or never resectable (unresectable extrahepatic disease). The former was deemed candidates for a conversion strategy in the presence of sufficient response; the latter was offered palliative chemotherapy.

CRLMs were defined as synchronous or metachronous according to Adam et al. [21]. Major hepatectomy was defined by the resection of four or more segments according to Reddy [22]. Progression-free survival (PFS) was defined as the duration from the beginning of the first-line treatment to disease progression, to death resulting from any cause, or to the last contact. Overall survival (OS) was defined as the duration between the beginning of first-line treatment to death resulting from any cause or to the last contact. For PFS as well as OS, patients without events were considered censored at the time of their last follow-up.

The primary endpoint was to compare survival outcomes (OS and PFS) of patients undergoing systemic treatment not leading to liver resection and that of surgically resected patients. Furthermore, we explored survival outcomes of ultimately resectable and potentially resectable patients.

As secondary endpoints, we investigated whether survival outcomes were different between patients whose strategy was discussed or not in MDT. As an exploratory outcome, we investigated eventual survival differences among unresected, ultimately resectable, and potentially resectable patients by stratifying these subgroups for induction ST regimen.

Patients with missing survival and recurrence information were excluded from data collection.

2.3. Statistical Analysis

Sample distribution was evaluated with Kolmogorov–Smirnov and Shapiro–Wilk tests. Continuous variables were compared by Kruskal–Wallis or ANOVA when appropriate, while categorical variables were analyzed using Pearson’s chi-squared test. Tests were adjusted for all pairwise comparisons using the Bonferroni correction.

Survival curves were obtained through the Kaplan–Meier method, and log-rank test was used to evaluate differences in cumulative survival among groups. A logistic regression model was built to detect independent predictors of outcome and to estimate the adjusted odds ratio (OR) and 95% confidence interval (95% CI). Only significant ($p < 0.1$) variables in the univariate analysis were included in the multivariate model. The median period of follow-up was calculated through the reverse Kaplan–Meier method. p values below 0.05 were considered statistically significant. Data were recorded in a computerized spreadsheet (Microsoft Excel 2016; Microsoft Corporation, Redmond, WA, USA) and analyzed with statistical software (IBM Corp., released 2021, IBM SPSS Statistics for Windows, Version 27.0; Armonk, NY, USA, IBM Corp.).

3. Results

3.1. Descriptive Statistics of the Sample

From March 2012 to October 2018, data have been recorded from 690 patients diagnosed with left-sided RAS/BRAF wild-type mCRC and treated with EGFRi-based first-line doublet chemotherapy. Three-hundred ninety-eight patients did not meet the inclusion criteria, and two-hundred ninety-two patients had liver-limited disease. Among these, 232 patients were judged as unresectable at diagnosis, but eventually, 56 of them had radical liver resection. Therefore, the proportion of patients undergoing chemotherapy leading to surgery with a curative intent (conversion rate) was 24.1%.

Further information is reported in the flow diagram depicting patients’ selection (Figure 1).

Among patients with liver-limited metastatic disease, only 96 (32.5%) underwent liver resection. Within this subgroup, 40 (41.7%) patients were deemed potentially resectable at diagnosis, whereas 56 (58.3%) patients were classified as ultimately resectable.

All patients initially identified as potentially resectable were eventually resected.

Compared to unresected patients, patients within the ultimately resectable cohort were more likely to be male ($p = 0.03$); ultimately and potentially resectable patients had a

significantly greater proportion of primary tumor resected ($p < 0.001$); unresected patients had greater nodal involvement ($p = 0.002$) and a higher burden of liver disease (proportion of >10 metastases at diagnosis— $p < 0.001$); and moreover, unresected patients had greater frequency of baseline CEA > 100 ng/mL compared to potentially resectable ones ($p = 0.016$). Further characteristics of the sample are reported in Table 1.

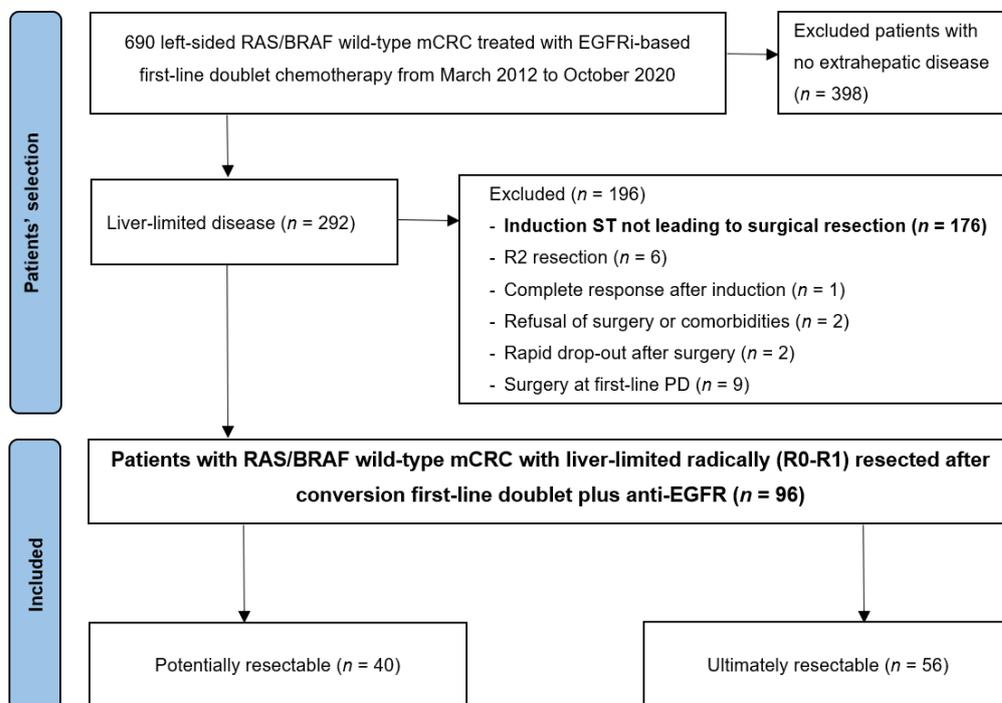


Figure 1. Flow diagram with patients' selection and disposition. Three out of six R2 patients were resected with a palliative intent. ST: systemic treatment.

Table 1. Clinicopathological, preoperative, and surgical characteristics of CRLM patients undergoing liver resection.

Variable	Induction ST Not Leading to Surgery (n = 176) N (%)	Ultimately Resectable (n = 56) N (%)	Potentially Resectable (n = 40) N (%)	Total (n = 272) N (%)	p
Age (median/IQR)	65 (57.3–72.7)	62 (52.8–70.7)	62.5 (57.2–69.7)	64 (56–71)	0.34
Male gender	110 (62.5)	46 (81.1) †	29 (72.5)	185 (68.0)	0.03
Site of primary tumor (rectum)	54 (30.7)	21 (38.9)	17 (44.7)	92 (34.3)	0.186
Histology (mucinous)	31 (18.5)	3 (5.7)	7 (18.4)	41 (15.8)	0.075
Grading					0.63
G1	7 (5.0)	1 (2.1)	1 (3.2)	9 (4.1)	
G2	96 (68.1)	38 (79.2)	21 (67.7)	155 (70.5)	
G3	38 (27.0)	9 (18.8)	9 (29.0)	56 (25.5)	
Primary tumor resected	115 (65.7)	52 (96.3) †	36 (94.7) ‡	203 (76.0)	<0.001
N+	65 (36.9) ^ * ‡	10 (18.5)	5 (13.2)	80 (29.9)	0.002
N° of liver metastases at diagnosis					<0.001
1	9 (5.1)	5 (8.9)	10 (25.0) ‡	24 (8.8)	
2–5	57 (32.4)	28 (50.0)	22 (55.5) ‡	107 (39.3)	
6–10	32 (18.2)	9 (16.1)	3 (7.5)	44 (16.2)	
>10	59 (33.5) * ‡	13 (23.2)	4 (10)	76 (27.9)	
Synchronous disease	150 (85.2)	45 (80.4)	28 (70.0)	223 (82.0)	0.073
Treatment approach discussed at MDT					0.921
ECOG 0	103 (58.5)	40 (71.4)	31 (32.3)	171 (63.8)	0.089

CEA at baseline (>100 ng/mL)	60 (37.5) *	15 (30)	4 (12.1)	79 (32.5)	0.016
HER-2 status					0.069
Not amplified	25 (14.2)	15 (27.8)	3 (7.8)	43 (16)	
Amplified	3 (1.7)	1 (1.9)	0	4 (1.5)	
Not evaluated	148 (84.1)	38 (70.4)	35 (92.1)	221 (82.5)	
N° of criteria for biologically challenging disease (median/IQR)	3 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)	0.075
Major liver resection	-	30 (56.6)	13 (34.2)	43 (44.8)	0.038
R0 resection	-	39 (78)	34 (89.5)	73 (76.0)	0.293
ST regimen					0.49
FOLFIRI + Cetuximab	71 (40.3)	21 (37.5)	20 (51.3)	112 (41.5)	
FOLFOX + Cetuximab	23 (13.1)	5 (8.9)	2 (5.1)	30 (11.1)	
FOLFIRI + Panitumumab	12 (6.8)	3 (5.4)	1 (2.6)	16 (5.9)	
FOLFOX + Panitumumab	70 (39.8)	27 (48.2)	15 (38.5)	112 (41.5)	
Number of ST cycles administered before surgical resection (median/IQR)	5 (1.5–10.5)	8 (6–12)	6 (0–8)	7 (5–10)	0.002 *
3 months PFS	167 (94.9)	56 (100)	40 (100)	263 (96.7)	0.083
6 months PFS	138 (78.4)	54 (98.2) †	37 (97.4) ‡	229 (85.1)	<0.001
10 months PFS	95 (54.0)	46 (83.6) †	34 (89.5) ‡	175 (65.1)	<0.001

PFS: Progression Free Survival; ECOG: Eastern Cooperative Oncology Group; ST: Systemic Treatment; SD: Standard Deviation; IQR: Interquartile range; * pairwise comparison favoring ultimately resectable over potentially resectable; † pairwise comparison favoring ultimately resectable over induction CT not leading to surgery; ‡ pairwise comparison favoring potentially resectable over induction CT not leading to surgery; ^ pairwise comparison favoring induction CT not leading to surgery over ultimately resectable; § pairwise comparison favoring induction CT not leading to surgery over potentially resectable. Significant *p*-values are evidenced in bold.

3.2. Primary Endpoint

The median period of follow-up was 35.4 months (95% CI: 30.6–40.2) in the overall population, 33.8 months (95% CI: 26.1–41.4) for patients undergoing ST not leading to surgery, 34.5 months (95% CI: 27.1–41.9) for the ultimately resectable group, and 43.9 months (95% CI: 35.2–52.6) for the potentially resectable group.

Patients undergoing liver resection after induction ST had a remarkable survival advantage compared to those receiving ST not leading to surgery (Log Rank test $p < 0.001$). The 5-year OS was 60.8% and 11.7%, respectively, (HR = 0.273; 95% CI: 0.16–0.46; $p < 0.001$). The former group had a median OS that was more than double compared to the latter (79.4 months, 95% CI: *not reached* vs. 28.0 months, 95% CI: 22.14–33.93). Potentially resectable patients had 71.1% of 5-year OS and demonstrated a significant survival advantage compared to patients not leading to resection (Log Rank test $p < 0.001$. HR = 0.443; 95% CI: 0.32–0.62; $p < 0.001$). The median OS was 94.5 months (95% CI: 49.95–139.19). Compared to those belonging to the ultimately resectable group, no survival differences were observed (Log Rank test $p = 0.311$. HR = 0.671; 95% CI: 0.31–1.46; $p = 0.314$).

Similarly, ultimately resectable patients had a significantly higher PFS compared to those receiving ST not leading to surgery (Log Rank test $p < 0.001$). The 5-year PFS was 22.2% and 6.3%, respectively (HR = 0.447; 95% CI: 0.32–0.63; $p < 0.001$). Ultimately resectable patients had a median PFS of 19 months (95% CI: 14.85–23.18), whereas the median was 12.4 months (95% CI: 10.75–14.02) for unresected patients. The 5-year PFS for potentially resectable patients was 25.7%, with a median PFS time of 24.3 months (95% CI: 15.27–33.35). No difference in PFS was observed compared to patients belonging to the ultimately resectable group (Log Rank test $p = 0.305$. HR = 0.782; 95% CI: 0.49–1.25; $p = 0.306$), although it was significantly higher compared to unresected patients (Log Rank test $p < 0.001$. HR = 0.605; 95% CI: 0.49–0.75; $p < 0.001$). Kaplan–Meier curves depicting 5-year OS and PFS are reported in Figure 2. Survival outcomes of R2 patients are reported in the Supplementary Materials (Figures S1–S4).

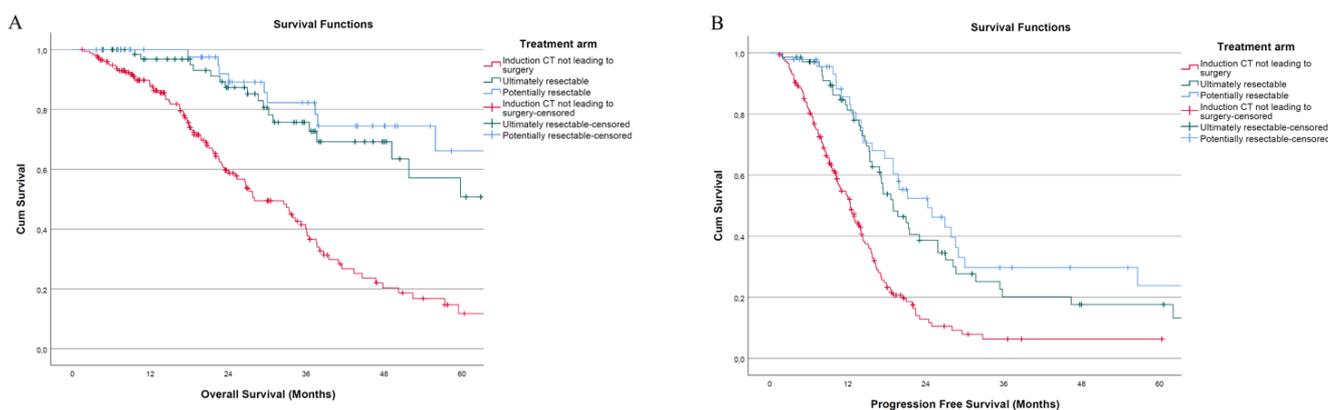


Figure 2. Kaplan–Meier curves of different treatment arms: (A) 5-year OS; (B) 5-year PFS.

3.3. Secondary Endpoints

Despite the improved 5-year OS for patients whose treatment strategy was discussed in MDT compared to their counterparts not discussed in MDT (14% vs. 0% for unresected patients; 61.9% vs. 60% for ultimately resectable; 75.7% vs. 60%—at 48 months—for potentially resectable), pairwise Kaplan–Meier analysis demonstrated significant differences only in the potentially resectable group (Log Rank test $p = 0.641$ for unresected patients; = 0.743 for ultimately resectable; = 0.012 for potentially resectable) (Figure 3A–C).

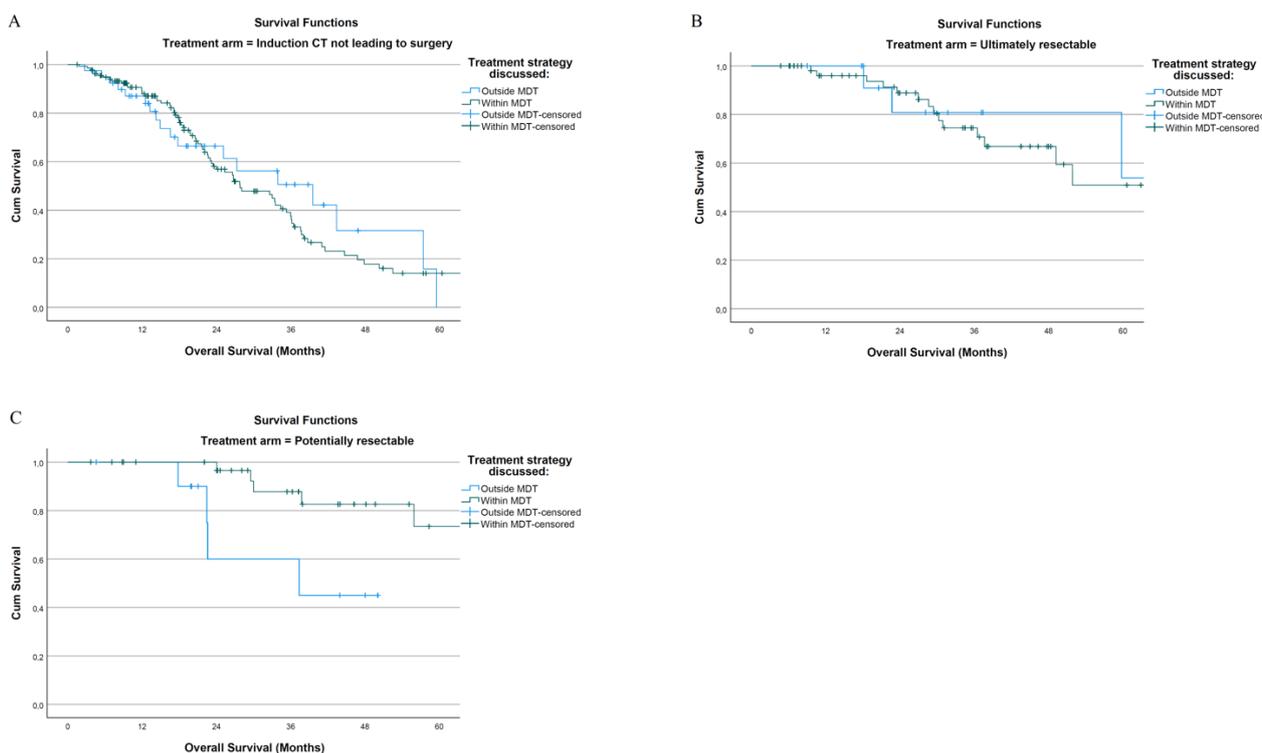


Figure 3. Kaplan–Meier curves of patients discussed or not in MDT—5-year OS of (A) unresected patients; (B) ultimately resectable patients; (C) potentially resectable patients.

There was no difference in 5-year PFS highlighted among the three groups (Log Rank test $p = 0.345$ for unresected patients; =0.936 for ultimately resectable; =0.243 for potentially resectable) (Kaplan–Meier curves are reported in the Supplementary Materials–Figure S5).

Compared to unresected patients, a survival advantage (for both OS and PFS) was noticed for patients belonging to potentially and ultimately resectable groups and

receiving either FOLFIRI- or FOLFOX-based I line ST regimens. However, patients receiving FOLFIRI-based regimens had a significant survival benefit compared to their counterparts receiving FOLFOX (Log-rank test $p = 0.039$). Five-year OS and PFS Kaplan–Meier curves are reported in the Supplementary Materials (Figure S6 and S7).

4. Discussion

In the present multicenter cohort study, 292 patients with RAS/BRAF wild-type liver-limited metastatic disease starting from left-sided CRC were analyzed. Fifty-six patients initially judged as non-surgical candidates eventually underwent hepatic resection with a conversion rate of 24.14%. A survival advantage was demonstrated for these patients over those receiving ST not leading to surgery.

Although our findings may not appear original, the present study may represent a valuable confirmation of current international guidelines. Multiple high-volume RCTs enrolled mCRC patients treated with doublets or triplets regimens, with or without surgical resection. Nevertheless, in most cases, these studies included both patients suffering from left- and right-sided colon cancer, regardless of RAS/BRAF mutational status. In our study, only a highly selected cohort of patients with left-sided and RAS/BRAF wild-type tumors was included, with survival outcomes way above the average reported in other trials.

In addition, there was no difference demonstrated between patients receiving peri-operative ST (potentially resectable) and ultimately resectable.

In this regard, it is worth noting that patients included in our study were all potentially resectable or non-resectable at diagnosis. This means that upfront surgery was not indicated, and patients were offered first-line medical treatment including EGFRi. Indeed, as demonstrated by the results of the New EPOC trial, in mCRC patients with resectable liver disease, the standard of care should be chemotherapy without monoclonal antibodies [23]. In contrast to our study, the New EPOC trial included patients that had a suboptimally resectable disease at diagnosis. Moreover, the New EPOC trial included only KRAS wild-type mCRC patients; meanwhile, our study included patients with both RAS and BRAF wild-type status.

In past years, conversion chemotherapy has led to surgical resection in up to 14% of cases [24–26]. In the PRIME trial, the complete resection rate for patients with KRAS WT mCRC was 10% (31 of 325 patients) in the panitumumab–FOLFOX4 arm [24]. In the PEAK trial, patients with RAS WT tumors receiving panitumumab + mFOLFOX6 had longer PFS (12.8 vs. 10.1 months, $p = 0.029$) and duration of response (11.4 vs. 9.0 months, $p = 0.011$) compared to those receiving bevacizumab + mFOLFOX6. The resection rates were similar between treatment arms (14 vs. 11%) [27].

In the last three years, several trials have demonstrated the possibility of increasing the proportion of patients converting to resectability [28–34].

Although many studies have tried to detect differences in survival related to the first-line chemotherapeutic backbone, the definition of the optimal ST regimen is still a matter of debate. Our results suggest that resected patients have a survival benefit compared to their unresected counterparts regardless of the subtype of doublet regimen. Nevertheless, looking more thoroughly at the ultimately resectable subgroup, patients receiving EGFRi/FOLFIRI-based regimens had a significant survival advantage compared to those receiving EGFRi/FOLFOX.

Compared to recent RCTs based on doublets with EGFRi/anti-VEGF, our results appear to be consistent. In the BECOME trial, the rate of conversion to surgery of patients treated with mFOLFOX6 plus Bevacizumab reached 23.1% [29]. In this trial, the OS and PFS of patients undergoing ST leading to surgery were 59.2% and 22.2%, respectively. In our study, the 5-year OS was 60.8% and the 5-year PFS was 22.2%. The median OS and PFS of these patients were 37.8 months and 7.8 months, which is remarkably lower compared to the 79.4 months OS and 21.5 months PFS of our study population. Nevertheless,

it should be noted that the BECOME trial enrolled not only left-sided CRLM patients but, more importantly, RAS-mutated patients.

Looking at the results of a recent retrospective study conducted at the Karolinska University Hospital [35], 31 patients over 100 receiving conversion ST became eligible for liver resection. Despite a higher conversion rate, 5-year OS and PFS, and median OS and PFS of the three groups (unresected, resected after conversion ST, and resected after neoadjuvant ST) were inferior. For completeness, it is worth mentioning that the study by Villard et al. included both right- and left-sided primary tumors and RAS/BRAF-mutated patients.

While research on optimal conversion ST is still on-going, different RCTs explored the impact of triplet regimens on survival outcomes and tumor response. Highly effective regimens, mainly based on FOLFOXIRI in association with Bevacizumab, led patients (initially unresectable) to being eligible for hepatectomy in up to 49% of cases, with a median PFS up to almost 32 months [31]. Notwithstanding, the efficacy of such intensive regimens is paid in terms of adverse events, especially ST-induced liver injury (steatohepatitis and sinusoidal damage), which may conflict with extensive hepatic resection. Therefore, as recommended by the most recent international guidelines [36], the main aim of any active metastatic systemic regimen should be obtaining sufficient downsizing of liver disease to allow for prompt surgical resection.

According to these principles, different studies have tried to explore the impact of several factors at the baseline evaluation that can stratify response to chemotherapy in terms of survival outcomes. In this scenario, Fong criteria were among the first to be proposed to predict cancer recurrence after liver resection, the encompassed nodal status, the number of CRLMs, the size of the largest metastasis, CEA level, and disease-free interval < 12 months after diagnosis of primary colorectal cancer [20]. In recent years, the GAME score has been presented and includes several other preoperative parameters (such as RAS mutational status and the presence of extrahepatic disease). The score outperformed Fong criteria in predicting overall survival of CRLM patients [37]. Finally, in 2020, the Comprehensive Evaluation of Relapse Risk (CERR) score was developed and validated. It evaluates the presence of KRAS, NRAS, and BRAF mutations, nodal status, CEA/CA19-9 levels, and the modified Tumor Burden Score to predict cancer recurrence. To this end, the CERR score was significantly superior to Fong and GAME scores in predicting overall survival [38].

In this setting, it would be compelling to explore the role of the parameters constituting the aforementioned tools to predict the conversion to resectability. We can argue that patients defined as low risk would be the ones who would best respond to induction ST. Therefore, in such cases, active doublet + EGFRi regimens with a lower toxicity profile would be preferable over more effective, but more toxic schemes, to achieve conversion to resectability. Indeed, patients with more aggressive tumor burden and biology would require more aggressive chemotherapy given the lower rates of conversion to resectability [24,25,39].

The enrollment of highly selected patients may have influenced our results. In our series, only patients suffering from left-sided CRLMs were included. The location of the primary tumor is currently a well-defined prognostic and predictive factor of response to EGFRi [5,40–42]. A recent meta-analysis highlighted how left-sided primaries achieve better outcomes (OS, PFS, and objective response rate) compared to right-sided primaries when ST plus EGFRi is administered.

In addition, patients enrolled in the present study were all RAS/BRAF wild type, which is another well-recognized positive prognostic factor. Furthermore, in our series, patients receiving induction ST not leading to surgery had significantly greater nodal involvement, hepatic disease load (in terms of number of liver metastases), and CEA levels at baseline which are all well-established predictors of worse outcomes.

The importance of multidisciplinary teams to improve survival outcomes of stage IV colorectal cancer patients is currently well-defined, and the involvement of experienced

hepatobiliary surgeons has demonstrated a trend leading towards higher resection rates and even more improved survival rates [3,36,43,44]. Surprisingly, in our series, no differences in OS and PFS were found between patients discussed within and outside MDT for each subgroup of patients. However, this result should not undermine the consolidated and remarkable effectiveness of multi-disciplinary teams; indeed, treatment strategy was decided outside MDT in only about 20% of cases, mostly belonging to unresected patients group. Thus, such a limited proportion may have influenced the lack of significant differences between the two groups.

Our study has limitations worth mentioning; first, its retrospective nature. The main issue is represented by the lack of a standardized definition of resectability. In 2006, Charnsangavej proposed three criteria to define resectability: preservation of at least two contiguous hepatic segments, adequate blood flow and biliary drainage, and >20% remnant liver of total liver volume. In our series, although in 78.1% of cases, the treatment strategy was discussed at MDT, it was not possible to determine whether the above-mentioned criteria were observed or not, or if other criteria were adopted to define resectability. Nevertheless, in all participant centers, a specialized hepato-biliary surgery unit was present; therefore, we can hypothesize that patients were evaluated by experienced liver surgeons, regardless of whether the assessment was provided within or outside MDT. According to Wei, the use of an MDT represents an important aspect of offering CRLM patients adequate and tailored treatment [45].

Another pitfall related to the retrospective nature of the study regards the subset of patients undergoing bowel resection first. To this end, it was not possible to define the reason for such a treatment approach (elective proper colectomy first or urgent/emergent colectomy for occlusion, perforation, and bleeding).

A further drawback of our study may be represented by the adoption of Fong criteria, which although valuable and widely used over the last two decades, have been developed more than twenty years ago. Unfortunately, we were not able to compute GAME and CERR scores due to the lack of several data parameters that were not collected because the aforementioned tools were first published only after the end of data collection.

Future Perspectives

Given the very poor survival outcomes of systemic therapy alone, growing evidence towards liver transplantation for even more strictly selected patients with nonresectable CRLM is being reported. Liver transplantation might be an additional therapeutic option for patients responding to induction ST but not achieving eligibility for resection, with a great advantage in terms of survival outcome compared to chemotherapy alone. Patient selection based on a combination of clinical and patho-radiological criteria (i.e., metabolic tumor volume and total lesion glycolysis on PET), molecular prognostic markers, and dynamic evaluation of biological behavior (assessment of response to bridging therapy during an extended period of observation time) guarantees 5-year OS ranging from 50% to 100% for unresectable liver disease [46–48]. Notably, the inclusion criteria for liver transplantation in ongoing trials enrolling unresectable CRLM are, like those described in our study, to identify patients that are eligible for successful conversion therapy.

However, there is little evidence to support liver transplantation over surgical resection for patients with resectable colorectal liver metastases after conversion therapy: if induction ST succeeds in making the patient resectable, surgical resection should be the preferred choice (even with sequential resection techniques such as two-stage hepatectomy and associating liver partition and portal vein ligation for staged hepatectomy) [49]. This is also true considering the shortage of donors and the unsolved problem of organ allocation.

5. Conclusions

Left-sided RAS/BRAF wild-type metastatic colorectal cancer patients with unresectable liver-limited disease at diagnosis may represent a subset of ideal candidates for tailored conversion strategies with the best available benefit–risk ratio, especially those with favorable biological behavior. Future prospective trials elucidating the role of different biological prognostic factors are needed to improve risk stratification.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/cancers14225513/s1>; Kaplan–Meier curves for OS including R2 resections with curative intent (page 2 supplementary file); Kaplan–Meier curves for PFS including R2 resections with curative intent (page 3 supplementary file); Kaplan–Meier curves for OS including all R2 resections (page 4 supplementary file); Kaplan–Meier curves for PFS including all R2 resections (page 5 supplementary file); Kaplan–Meier curves for PFS of patients discussed within and outside MDT (page 6 supplementary file); Kaplan–Meier curves for OS of patients receiving different I line ST regimens (page 8 supplementary file); and Kaplan–Meier curves for PFS of patients receiving different I line ST regimens (page 10 supplementary file).

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Informed Consent Statement: All patients alive at the time of data collection provided informed consent to participate to this retrospective observational non-interventional study. The procedures followed were in accordance with the precepts of Good Clinical Practice and the declaration of Helsinki.

Data Availability Statement: The datasets used during the present study are available from the corresponding authors upon reasonable request.

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References

1. Jegatheeswaran, S.; Mason, J.M.; Hancock, H.C.; Siriwardena, A.K. The liver-first approach to the management of colorectal cancer with synchronous hepatic metastases: A systematic review. *JAMA Surg.* **2013**, *148*, 385–391. <https://doi.org/10.1001/jamasurg.2013.1216>.
2. van de Velde, C.J.H. Treatment of liver metastases of colorectal cancer. *Ann. Oncol.* **2005**, *16*, 144–149. <https://doi.org/10.1093/annonc/mdi702>.
3. Van Cutsem, E.; Cervantes, A.; Adam, R.; Sobrero, A.; Van Krieken, J.H.; Aderka, D.; Aranda Aguilar, E.; Bardelli, A.; Benson, A.; Bodoky, G.; et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann. Oncol.* **2016**, *27*, 1386–1422. <https://doi.org/10.1093/annonc/mdw235>.
4. Associazione Italiana Oncologia Medica (AIOM). Linee Guida TUMORI DEL COLON. 2020. Available online: https://www.aiom.it/wp-content/uploads/2020/10/2020_LG_AIOM_Colon.pdf (accessed on 30 June 2022).
5. Arnold, D.; Lueza, B.; Douillard, J.-Y.; Peeters, M.; Lenz, H.-J.; Venook, A.; Heinemann, V.; Van Cutsem, E.; Pignon, J.-P.; Taberner, J.; et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. *Ann. Oncol.* **2017**, *28*, 1713–1729. <https://doi.org/10.1093/annonc/mdx175>.

6. Parisi, A.; Porzio, G.; Cannita, K.; Venditti, O.; Avallone, A.; Filippi, R.; Salvatore, L.; Tortora, G.; Ribelli, M.; Nigro, O.; et al. Clinicians' Attitude to Doublet Plus Anti-EGFR Versus Triplet Plus Bevacizumab as First-line Treatment in Left-Sided RAS and BRAF Wild-Type Metastatic Colorectal Cancer Patients: A Multicenter, "Real-Life", Case-Control Study. *Clin. Colorectal Cancer* **2021**, *20*, 318–325. <https://doi.org/10.1016/j.clcc.2021.07.003>.
7. Parisi, A.; Ghidini, M.; Giampieri, R.; Tomasello, G.; Luciani, A.; Ferri, C.; Berardi, R.; Petrelli, F. Post-induction Strategies in Metastatic Colorectal Cancer Patients Treated with First-Line Anti-EGFR-Based Treatment: A Systematic Review and Meta-Analysis. *Clin. Colorectal Cancer* **2022**, *21*, 162–170. <https://doi.org/10.1016/j.clcc.2021.12.005>.
8. Benson, A.B.; Venook, A.P.; Al-Hawary, M.M.; Arain, M.A.; Chen, Y.J.; Ciombor, K.K.; Cohen, S.; Cooper, H.S.; Deming, D.; Farkas, L.; et al. NCCN Guidelines for Colon Cancer. *JNCCN J. Natl. Compr. Cancer Netw.* **2021**, *19*. <https://doi.org/10.6004/jnccn.2021.0012>
9. Wang, L.; Sun, Y.; Zhao, B.; Zhang, H.; Yu, Q.; Yuan, X. Chemotherapy plus targeted drugs in conversion therapy for potentially resectable colorectal liver metastases: A metaanalysis. *Oncotarget* **2016**, *7*, 55732–55740. <https://doi.org/10.18632/oncotarget.9675>.
10. Ye, L.C.; Liu, T.S.; Ren, L.; Wei, Y.; Zhu, D.X.; Zai, S.Y.; Ye, Q.H.; Yu, Y.; Xu, B.; Qin, X.Y.; et al. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. *J. Clin. Oncol.* **2013**, *31*, 1931–1938. <https://doi.org/10.1200/JCO.2012.44.8308>.
11. Falcone, A.; Ricci, S.; Brunetti, I.; Pfanner, E.; Allegrine, G.; Barbara, C.; Crinò, L.; Benedetti, G.; Evangelista, W.; Fanchini, L.; et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: The gruppo oncologico nord ovest. *J. Clin. Oncol.* **2007**, *25*, 1670–1676. <https://doi.org/10.1200/JCO.2006.09.0928>.
12. Cremolini, C.; Casagrande, M.; Loupakis, F.; Aprile, G.; Bergamo, F.; Masi, G.; Moretto, R.R.; Pietrantonio, F.; Marmorino, F.; Zucchelli, G.; et al. Efficacy of FOLFOXIRI plus bevacizumab in liver-limited metastatic colorectal cancer: A pooled analysis of clinical studies by Gruppo Oncologico del Nord Ovest. *Eur. J. Cancer* **2017**, *73*, 74–84. <https://doi.org/10.1016/j.ejca.2016.10.028>.
13. Tomasello, G.; Petrelli, F.; Ghidini, M.; Russo, A.; Passalacqua, R.; Barni, S. FOLFOXIRI plus bevacizumab as conversion therapy for patients with initially unresectable metastatic colorectal cancer: A systematic review and pooled analysis. *JAMA Oncol.* **2017**, *3*, e170278. <https://doi.org/10.1001/jamaoncol.2017.0278>.
14. Adam, R.; Delvart, V.; Pascal, G.; Valeanu, A.; Castaing, D.; Azoulay, D.; Giacchetti, S.; Paule, B.; Kunstlinger, F.; Ghémard, O.; et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: A model to predict long-term survival. *Ann. Surg.* **2004**, *240*, 644–658. <https://doi.org/10.1097/01.sla.0000141198.92114.f6>.
15. Charnsangavej, C.; Clary, B.; Fong, Y.; Grothey, A.; Pawlik, T.M.; Choti, M.A. Selection of patients for resection of hepatic colorectal metastases: Expert consensus statement. *Ann. Surg. Oncol.* **2006**, *13*, 1261–1268. <https://doi.org/10.1245/s10434-006-9023-y>.
16. Kaczierek, K. ASCO 2016—Update colorectal liver metastases. *Memo-Mag. Eur. Med. Oncol.* **2017**, *10*, 103–105. <https://doi.org/10.1007/s12254-016-0308-y>.
17. González, H.D.; Figueras, J. Practical questions in liver metastases of colorectal cancer: General principles of treatment. *HPB* **2007**, *9*, 251–258. <https://doi.org/10.1080/13651820701457992>.
18. Bittoni, A.; Scartozzi, M.; Giampieri, R.; Faloppi, L.; Maccaroni, E.; Del Prete, M.; Bianconi, M.; Cascinu, S. The Tower of Babel of liver metastases from colorectal cancer: Are we ready for one language? *Crit. Rev. Oncol. Hematol.* **2013**, *85*, 332–341. <https://doi.org/10.1016/j.critrevonc.2012.08.005>.
19. Adam, R.; De Gramont, A.; Figueras, J.; Guthrie, A.; Kokudo, N.; Kunstlinger, F.; Loyer, E.; Poston, G.; Rougier, P.; Rubbia-Brandt, L.; et al. The Oncosurgery Approach to Managing Liver Metastases from Colorectal Cancer: A Multidisciplinary International Consensus. *Oncologist* **2012**, *17*, 1225–1239. <https://doi.org/10.1634/theoncologist.2012-0121>.
20. Fong, Y.; Fortner, J.; Sun, R.L.; Brennan, M.F.; Blumgart, L.H. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: Analysis of 1001 consecutive cases. *Ann. Surg.* **1999**, *230*, 309. <https://doi.org/10.1097/00000658-199909000-00004>.
21. Adam, R.; de Gramont, A.; Figueras, J.; Kokudo, N.; Kunstlinger, F.; Loyer, E.; Poston, G.; Rougier, P.; Rubbia-Brandt, L.; Sobrero, A.; et al. Managing synchronous liver metastases from colorectal cancer: A multidisciplinary international consensus. *Cancer Treat. Rev.* **2015**, *41*, 729–741. <https://doi.org/10.1016/j.ctrv.2015.06.006>.
22. Reddy, S.K.; Barbas, A.S.; Turley, R.S.; Steel, J.L.; Tsung, A.; Marsh, J.W.; Geller, D.A.; Clary, B.M. A standard definition of major hepatectomy: Resection of four or more liver segments. *HPB* **2011**, *13*, 494–502. <https://doi.org/10.1111/j.1477-2574.2011.00330.x>.
23. Bridgewater, J.A.; Pugh, S.A.; Maishman, T.; Emlinton, Z.; Mellor, J.; Whitehead, A.; Stanton, L.; Radford, M.; Corkhill, A.; Griffiths, G.O.; et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis (New EPOC): Long-term results of a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol.* **2020**, *21*, 398–411. [https://doi.org/10.1016/S1470-2045\(19\)30798-3](https://doi.org/10.1016/S1470-2045(19)30798-3).
24. Douillard, J.Y.; Siena, S.; Cassidy, J.; Tabernero, J.; Burkes, R.; Barugel, M.; Humblet, Y.; Bodoky, G.; Cunningham, D.; Jassem, J.; et al. Randomized, Phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) Versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: The PRIME study. *J. Clin. Oncol.* **2010**, *28*, 4697–4705. <https://doi.org/10.1200/JCO.2009.27.4860>.
25. Van Cutsem, E.; Köhne, C.-H.; Hitre, E.; Zaluski, J.; Chang Chien, C.-R.; Makhson, A.; D'Haens, G.; Pintér, T.; Lim, R.; Bodoky, G.; et al. Cetuximab and Chemotherapy as Initial Treatment for Metastatic Colorectal Cancer. *N. Engl. J. Med.* **2009**, *360*, 1408–1417. <https://doi.org/10.1056/nejmoa0805019>.

26. Adam, R.; Avisar, E.; Ariche, A.; Giachetti, S.; Azoulay, D.; Castaing, D.; Kunstlinger, F.; Levi, F.; Bismuth, F. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal [liver] metastases. *Ann. Surg. Oncol.* **2001**, *8*, 347–353. <https://doi.org/10.1245/aso.2001.8.4.347>.
27. Rivera, F.; Karthaus, M.; Hecht, J.R.; Sevilla, I.; Forget, F.; Fasola, G.; Canon, J.L.; Guan, X.; Demonty, G.; Schwartzberg, L.S. Final analysis of the randomised PEAK trial: Overall survival and tumour responses during first-line treatment with mFOLFOX6 plus either panitumumab or bevacizumab in patients with metastatic colorectal carcinoma. *Int. J. Colorectal Dis.* **2017**, *32*, 1179–1190. <https://doi.org/10.1007/s00384-017-2800-1>.
28. Oki, E.; Emi, Y.; Yamanaka, T.; Uetake, H.; Muro, K.; Takahashi, T.; Nagasaka, T.; Hatano, E.; Ojima, H.; Manaka, D.; et al. Randomised phase II trial of mFOLFOX6 plus bevacizumab versus mFOLFOX6 plus cetuximab as first-line treatment for colorectal liver metastasis (ATOM trial). *Br. J. Cancer* **2019**, *121*, 222–229. <https://doi.org/10.1038/s41416-019-0518-2>.
29. Tang, W.; Ren, L.; Liu, T.; Ye, Q.; Wei, Y.; He, G.; Lin, Q.; Wang, X.; Wang, M.; Liang, F.; et al. Bevacizumab plus mFOLFOX6 versus mFOLFOX6 alone as first-line treatment for RAS mutant unresectable colorectal liver-limited metastases: The BECOME randomized controlled trial. *J. Clin. Oncol.* **2020**, *38*, 3175–3184. <https://doi.org/10.1200/JCO.20.00174>.
30. Schmoll, H.; Garlipp, B.; Junghanß, C.; Vogel, A.; Kaiser, U.; Florschütz, A.; Kanzler, S.; Hannig, C.; Meinert, F.; Cygon, F.; et al. FOLFOX/bevacizumab +/- irinotecan in advanced colorectal cancer (CHARTA): Long term outcome. *Ann. Oncol.* **2018**, *29*, v108. <https://doi.org/10.1093/annonc/mdy149.022>.
31. Gruenberger, T.; Bridgewater, J.; Chau, I.; García Alfonso, P.; Rivoire, M.; Mudan, S.; Lasserre, S.; Hermann, F.; Waterkamp, D.; Adam, R. Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: The OLIVIA multinational randomised phase II trial. *Ann. Oncol.* **2015**, *26*, 702–708. <https://doi.org/10.1093/annonc/mdu580>.
32. Hurwitz, H.L.; Tan, B.R.; Reeves, J.A.; Xiong, H.; Somer, B.; Lenz, H.-J.; Hochster, H.S.; Scappaticci, F.; Palma, J.F.; Price, R.; et al. Phase II Randomized Trial of Sequential or Concurrent FOLFOXIRI-Bevacizumab Versus FOLFOX-Bevacizumab for Metastatic Colorectal Cancer (STEAM). *Oncologist* **2019**, *24*, 921–932. <https://doi.org/10.1634/theoncologist.2018-0344>.
33. Cremolini, C.; Loupakis, F.; Antoniotti, C.; Lupi, C.; Sensi, E.; Lonardi, S.; Mezi, S.; Tomasello, G.; Ronzoni, M.; Zaniboni, A.; et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: Updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *Lancet Oncol.* **2015**, *16*, 1306–1315. [https://doi.org/10.1016/S1470-2045\(15\)00122-9](https://doi.org/10.1016/S1470-2045(15)00122-9).
34. Cremolini, C.; Antoniotti, C.; Rossini, D.; Lonardi, S.; Loupakis, F.; Pietrantonio, F.; Bordonaro, R.; Latiano, T.P.; Tamburini, E.; Santini, D.; et al. Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2): A multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol.* **2020**, *21*, 497–507. [https://doi.org/10.1016/S1470-2045\(19\)30862-9](https://doi.org/10.1016/S1470-2045(19)30862-9).
35. Villard, C.; Habib, M.; Nordenvall, C.; Nilsson, P.J.; Jorns, C.; Sparrelid, E. Conversion therapy in patients with colorectal liver metastases. *Eur. J. Surg. Oncol.* **2021**, *47*, 2038–2045. <https://doi.org/10.1016/j.ejso.2021.02.019>.
36. National Comprehensive Cancer Network. NCCN Guidelines Version 1.2022 Colon Cancer. 2022. Available online: <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1428> (accessed on 28 July 2022).
37. Margonis, G.A.; Sasaki, K.; Gholami, S.; Kim, Y.; Andreatos, N.; Rezaee, N.; Deshwar, A.; Buettner, S.; Allen, P.J.; Kingham, T.P.; et al. Genetic And Morphological Evaluation (GAME) score for patients with colorectal liver metastases. *Br. J. Surg.* **2018**, *105*, 1210–1220. <https://doi.org/10.1002/bjs.10838>.
38. Chen, Y.; Chang, W.; Ren, L.; Chen, J.; Tang, W.; Liu, T.; Jian, M.; Liu, Y.; Wei, Y.; Xu, J. Comprehensive Evaluation of Relapse Risk (CERR) Score for Colorectal Liver Metastases: Development and Validation. *Oncologist* **2020**, *25*, e1031–e1041. <https://doi.org/10.1634/theoncologist.2019-0797>.
39. Heinemann, V.; von Weikersthal, L.F.; Decker, T.; Kiani, A.; Vehling-Kaiser, U.; Al-Batran, S.-E.; Heintges, T.; Lerchenmüller, C.; Kahl, C.; Seipelt, G.; et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): A randomised, open-label, phase 3 trial. *Lancet Oncol.* **2014**, *15*, 1065–1075. [https://doi.org/10.1016/S1470-2045\(14\)70330-4](https://doi.org/10.1016/S1470-2045(14)70330-4).
40. Venook, A.P.; Niedzwiecki, D.; Innocenti, F.; Fruth, B.; Greene, C.; O’Neil, B.H.; Shaw, J.E.; Atkins, J.N.; Horvath, L.E.; Polite, B.N.; et al. Impact of primary (1°) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance). *J. Clin. Oncol.* **2016**, *34*, 3504. https://doi.org/10.1200/jco.2016.34.15_suppl.3504.
41. Yahagi, M.; Okabayashi, K.; Hasegawa, H.; Tsuruta, M.; Kitagawa, Y. The Worse Prognosis of Right-Sided Compared with Left-Sided Colon Cancers: A Systematic Review and Meta-analysis. *J. Gastrointest. Surg.* **2016**, *20*, 648–655. <https://doi.org/10.1007/s11605-015-3026-6>.
42. Wang, F.; Bai, L.; Liu, T.S.; Yu, Y.Y.; He, M.M.; Liu, K.Y.; Luo, H.Y.; Zhang, D.S.; Jin, Y.; Wang, F.H.; et al. Right- and left-sided colorectal cancers respond differently to cetuximab. *Chin. J. Cancer* **2015**, *34*, 24. <https://doi.org/10.1186/s40880-015-0022-x>.
43. Engstrand, J.; Kartalis, N.; Strömberg, C.; Broberg, M.; Stillström, A.; Lekberg, T.; Jonas, E.; Freedman, J.; Nilsson, H. The Impact of a Hepatobiliary Multidisciplinary Team Assessment in Patients with Colorectal Cancer Liver Metastases: A Population-Based Study. *Oncologist* **2017**, *22*, 1067–1074. <https://doi.org/10.1634/theoncologist.2017-0028>.

44. Lan, Y.T.; Jiang, J.K.; Chang, S.C.; Yang, S.H.; Lin, C.C.; Lin, H.H.; Wang, H.S.; Chen, W.S.; Lin, T.C.; Lin, J.K. Improved outcomes of colorectal cancer patients with liver metastases in the era of the multidisciplinary teams. *Int. J. Colorectal Dis.* **2016**, *31*, 403–411. <https://doi.org/10.1007/s00384-015-2459-4>.
45. Wei, A.C.; Jarnagin, W.R. Questioning Why More Patients with Colorectal Liver Metastases Are Not Referred for Metastasectomy. *JAMA Surg.* **2020**, *155*, 909. <https://doi.org/10.1001/jamasurg.2020.1460>.
46. Dueland, S.; Grut, H.; Syversveen, T.; Hagness, M.; Line, P.D. Selection criteria related to long-term survival following liver transplantation for colorectal liver metastasis. *Am. J. Transplant.* **2020**, *20*, 530–537. <https://doi.org/10.1111/ajt.15682>.
47. Dueland, S.; Smedman, T.M.; Røsok, B.; Grut, H.; Syversveen, T.; Jørgensen, L.H.; Line, P.D. Treatment of relapse and survival outcomes after liver transplantation in patients with colorectal liver metastases. *Transpl. Int.* **2021**, *34*, 2213–2250. <https://doi.org/10.1111/tri.13995>.
48. Varley, R.; Tarazi, M.; Davé, M.; Mobarak, S.; Stott, M.C.; Baltatzis, M.; Satyadas, T. Liver Transplantation for Non-Resectable Liver Metastases from Colorectal Cancer: A Systematic Review and Meta-Analysis. *World J. Surg.* **2021**, *45*, 3404–3413. <https://doi.org/10.1007/s00268-021-06248-4>.
49. Bonney, G.K.; Chew, C.A.; Lodge, P.; Hubbard, J.; Halazun, K.J.; Trunecka, P.; Muiesan, P.; Mirza, D.F.; Isaac, J.; Laing, R.W.; et al. Liver transplantation for non-resectable colorectal liver metastases: The International Hepato-Pancreato-Biliary Association consensus guidelines. *Lancet Gastroenterol. Hepatol.* **2021**, *6*, 933–946. [https://doi.org/10.1016/S2468-1253\(21\)00219-3](https://doi.org/10.1016/S2468-1253(21)00219-3).