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Radiologic and pathologic response to neoadjuvant chemotherapy predicts survival in patients undergoing the liver-first approach for synchronous colorectal liver metastases☆

Giammauro Berardi [a], Marc De Man [b], Stéphanie Laurent [b], Peter Smeets [c], Federico Tomassini [a], Riccardo Ariotti [a], Anne Hoorens [d], Jo van Dorpe [d], Oswald Varin [e], Karen Geboes [b], Roberto I. Troisi [a, f, *]

[a] Dept. of General Hepatobiliary and Liver Transplantation Surgery, Ghent University Hospital and Medical School, C. Heymanslaan 10, Ghent 9000, Belgium
[b] Dept. of Oncology, Ghent University Hospital and Medical School, Ghent, Belgium
[c] Dept. of Radiology, Ghent University Hospital and Medical School, Ghent, Belgium
[d] Dept. of Pathology, Ghent University Hospital and Medical School, Ghent, Belgium
[e] Dept. of Gastroenterology, Ghent University Hospital and Medical School, Ghent, Belgium
[f] Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy

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ABSTRACT

Purpose: To investigate the short- and long-term outcomes of liver first approach (LFA) in patients with synchronous colorectal liver metastases (CRLM), evaluating the predictive factors of survival.
Methods: Sixty-two out of 301 patients presenting with synchronous CRLM underwent LFA between 2007 and 2016. All patients underwent neoadjuvant chemotherapy. After neoadjuvant treatment patients were re-evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST). Liver resection was scheduled after 4–6 weeks. Changes in non-tumoral parenchyma and the tumor response according to the Tumor Regression Grade score (TRG) were assessed on surgical specimens. Primary tumor resection was scheduled 4–8 weeks following hepatectomy.
Results: Five patients out of 62 (8.1%) showed "Progressive Disease" at re-evaluation after neoadjuvant chemotherapy, 22 (35.5%) showed "Stable Disease" and 35 (56.5%) "Partial Response"; of these latter, 29 (82%) showed histopathologic downstaging. The 5-year survival (OS) rate was 55%, while the 5-year disease-free survival (DFS) rate was 16%. RECIST criteria, T-stage, N-stage and TRG were independently associated with OS. Bilobar presentation of disease, RECIST criteria, R1 margin and TRG were independently associated with DFS. Patients with response to neoadjuvant chemotherapy had better survival than those with stable or progressive disease (radiological response 5-y OS: 65% vs. 50%; 5-y DFS: 20% vs. 10%; pathological response 5-y OS: 75% vs. 56%; 5-y DFS: 45% vs. 11%).
Conclusions: LFA is an oncologically safe strategy. Selection is a critical point, and the best results in terms of OS and DFS are observed in patients having radiological and pathological response to neoadjuvant chemotherapy.
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Introduction

Colorectal cancer (CRC) still represents the third most common cancer worldwide, and 25% of patients present with liver metastases (CRLM) at the time of diagnosis [1,2]. Synchronous presentation of metastatic disease to the liver is a predictor of worse prognosis [3,4]. However, cure is possible, and survival has improved over the years, especially because of the introduction of a multimodal approach, including the use of targeted agents, modern chemo (-radio) therapy and liver resection [5].

Resection is considered the only curative option for patients with colorectal cancer and synchronous metastases [6,7]. Currently, three different approaches are available: the classical approach, combined approach and liver-first approach (LFA).

☆ GB is a fellow from "Sapienza" University of Rome.

* Corresponding author. Dept. of General Hepatobiliary and Liver Transplantation Surgery, Ghent University Hospital and Medical School, C. Heymanslaan 10, Ghent 9000, Belgium.
E-mail address: roberto.troisi@ugent.be (R.I. Troisi).

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The classical strategy includes resection of the primary tumor followed by systemic chemotherapy and delayed hepatic surgery. The main drawback is the possible progression of the disease in the liver, rendering CRLM unresectable; this is especially of concern in patients who develop complications after colorectal surgery, delaying the administration of chemotherapy and subsequent liver resection [8].

Simultaneous resection has been successfully reported in selected patients [9,10]. However, this strategy remains associated with increased complications when major hepatectomy or complex surgery of the primary tumor is needed [11–13].

Based on the well-known benefits of chemotherapy in terms of the survival and response rates [14,15], and since the prognosis of patients is mainly driven by the metastatic disease rather than the primary tumor, in 2006, Mentha et al. described LFA in which chemotherapy is given first, followed by liver surgery and finally colorectal cancer resection [16–18].

The rationale behind LFA is the rapid administration of systemic therapy: this can turn unresectable disease into resectable due to the high response rates induced with modern regimens. Second, delays in the treatment of systemic disease are avoided [19,20]. Furthermore, systemic treatment could be considered a "test of time", giving some clues concerning tumor biology, and eventually sparing unnecessary surgery [21,22].

In a recent meta-analysis comparing classical, combined and liver-first surgical strategies, no differences in terms of mortality, morbidity and overall survival were evident among the 3 approaches [23]. However, due to the low caseload compared with the other two groups, no clear and definitive results could be drawn concerning LFA.

This study was designed to investigate the outcomes of LFA in patients with stage IV colorectal cancer with synchronous liver metastases focusing on clinical, radiological and histopathological characteristics and their influence on survival.

Materials and methods

From January 2007 to September 2016, 637 liver resections for CRLM were performed. Three hundred one (47.2%) of these patients presented with synchronous liver disease at diagnosis. After a multidisciplinary team discussion involving liver surgeons, colorectal surgeons, oncologists, gastroenterologists, pathologists and radiologists, the best therapeutic strategy was decided on a case-by-case basis. Patients were selected for a "Classical Strategy" in the case of symptomatic primary disease (obstruction, bleeding, perforation), for a "Combined Resection" when minor surgeries on the colon (right/left hemicolectomy) and liver (wedge resections, left lateral sectionectomy, segmentectomy) were feasible, and for a "Liver First Approach" when an asymptomatic colorectal tumor was present and a borderline resectable or upfront unresectable liver disease was diagnosed. These institutional guidelines were not clearly defined but rather adapted to the patient and disease.

Eighty-one patients underwent LFA, and only patients with a minimum follow-up of 2 years were selected. Patients with extrahepatic disease were excluded. Finally, 62 patients fulfilled the selection criteria (Table 1). The hospital charts of these patients were retrospectively reviewed; Ethical Committee approval was not needed for the study.

Patients were divided into "Resectable", "Unresectable", and "Non-optimally Resectable" with respect to CRLM. Resection resulting in insufficient future liver remnant (<40%) was considered as "Unresectable" disease. Bilobar disease and/or large lesions (>5 cm) and/or multiple lesions (>4), located close to the liver hilum or adjacent to main vessels were considered as "Non-optimally Resectable". Microwave ablation (MWA) was considered in some

Table 1
Patient's perioperative characteristics.

	N = 62
Gender (F/M)	22/40
Age >70y	14 (22%)
Mean	60.6 ± 11
ASA score (I–II–III)	9–31–22
Preoperative CEA (ng/ml)	25 (2–1282)
Bilobar Disease	43 (69%)
Number of lesions ≥3	41 (66%)
Mean	3.9 ± 3
Lesions size ≥50 mm	27 (43%)
Mean	54.2 ± 38
Non-Optimally Resectable/Unresectable at diagnosis	50 (81%)
Neoadjuvant Chemotherapy	62 (100%)
FOLFOX/FOLFIRI	40/22
Biological Drug[a]	42 (68%)
Neoadjuvant Radiotherapy	42 (68%)
Type of Resection	
Wedge resection	22 (35%)
Monosegmentectomy	7 (11%)
Bisegmentectomy	3 (5%)
Right hepatectomy	7 (11%)
Right extended hepatectomy	1 (2%)
Left Hepatectomy	3 (5%)
Left Lateral sectionectomy	5 (8%)
Resections + Microwave Ablations (MWA)	14 (23%)
Primary site	
Right Colon	4 (6%)
Left Colon/Sigma	11 (18%)
Rectum	47 (76%)
Primary Surgery	47/62 (76%)
Right hemicolectomy	3 (6%)
Left hemicolectomy/Sigmoidectomy	16 (34%)
Anterior Rectum Resection	25 (53%)
Abdominoperineal Resection	3 (6%)
Primary T stage	
pT1	1 (1.6%)
pT2	11 (17.7%)
pT3	25 (40.3%)
pT4	10 (16.1%)
Primary N stage	
pN0	18 (29%)
pN1	16 (25.8%)
pN2	9 (14.5%)
pN3	4 (6.4%)
Steatohepatitis	
Kleiner score 0/1/2	55 (88.7%)
Kleiner score 3/4	6 (9.7%)
Kleiner score 5/6/7/8	1 (1.6%)
Fibrosis	
F0	37 (59.7%)
F1a	17 (27.4)
F1b	0
F1c	3 (4.8%)
F2	5 (8.1%)
Sinusoidal dilation	
0 = Absent	32 (51.6%)
1 = Mild	13 (21%)
2 = Moderate	12 (19.4%)
3 = Severe	5 (8.1%)
Nodular Regenerative Hyperplasia	
0 = Absent	40 (64.5%)
1 = Present but indistinct	9 (14.5%)
2 = Present but occasionally distinct	9 (14.5%)
3 = Distinct in most examined areas	4 (6.5%)
Tumor Regression Grade	
1 = Absence of residual cancer and large amount of fibrosis	1 (1.6%)
2 = Rare residual cancer cells scattered throughout the fibrosis	10 (16.1%)
3 = More residual tumor cells but fibrosis predominates	25 (40.3%)
4 = Residual cancer cells predominate over fibrosis	24 (38.7%)
5 = No signs of regression	2 (3.2%)

[a] Considering Bevacizumab or Cetuximab; °3 left hepatectomies + wedge resections, 2 left lateral sectionectomies + wedge resections, 2 right hepatectomies + wedge resections, 3 segmentectomies + wedge resections, 3 wedge resections + MWA of 2 other lesions/each and 1 left lateral sectionectomy + 3 additional MWA. CEA, Carcinoembryonic Antigen.

cases to reduce tumor burden by treating lesions smaller than 3 cm in size aiming to a parenchyma-preserving surgery.

All patients underwent neoadjuvant chemotherapy regardless being upfront resectable with FOLFIRI or FOLFOX with or without biological agent based on the RAS status, extension of disease and toxicity profiles. In the case of T3N0 or N+ low rectal tumors, either a short-course (5 × 5 Gy) of radiation or a long course of 28 fractions of 1.8-Gy radiation with capecitabine followed by preoperative chemotherapy was considered. Re-evaluation was performed 2–3 weeks after the last administration of chemotherapy to further classify patients according to the New Response Evaluation Criteria in Solid Tumors (RECIST) [24].

Liver resection was performed 4–6 weeks after the last cycle of chemotherapy.

For pathological assessment, all archived slides of the liver resections were reviewed. Specimens were sectioned in 0.5-cm-thick slides. Samples were taken from all metastases, as well as non-tumoral tissue. The pathological tumor response was evaluated according to the tumor regression grade (TRG) with slight modifications, considering infarct-like-necrosis and acellular mucin pools in the case of mucinous carcinomas (Supplemental Table) [25–29]. For the assessment of non-tumoral liver tissue, HE, Sirius red, Masson's trichrome, PAS-diastase, Perls and reticulin staining were performed, as well as keratin 7 immunohistochemistry. Steatohepatitis and fibrosis were scored according to Kleiner [30]. Sinusoidal dilation (SOS) was graded as follows: 0, absent; 1, mild; 2, moderate; 3, severe [31]. Nodular regenerative hyperplasia (NRH) was graded according to the Wanless scoring system [32].

Primary tumor resection was scheduled 4–8 weeks following liver resection or after the completion of chemotherapy.

Statistical analysis

Overall survival (OS) was considered as the time from liver resection to death or the last follow up. Disease-free survival (DFS) was considered as the time between liver resection and recurrence

Table 2
Predictive factors for overall survival.

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)*	P Value	OR (95% CI)	P Value
Female Sex	0.82 (0.633–2.03)	0.67		
Age	1.02 (0.98–1.07)	0.26		
Bilobar Disease	1.35 (0.48–3.78)	0.56		
N Lesions	1.15 (1.01–1.33)	0.03	1.03 (0.98–1.07)	0.15
Size Lesions	0.99 (0.97–1.00)	0.24		
Upfront resectable at diagnosis	0.78 (0.23–2.61)	0.68		
Association of Biological drugs	0.75 (0.30–1.88)	0.54		
Radiotherapy	1.03 (0.41–2.61)	0.93		
CEA	0.99 (0.99–1.00)	0.41		
RECIST Progressive Disease	1	0.001	1	0.01
Stable Disease	0.63 (0.23–0.99)		0.42 (0.13–0.73)	
Partial Response	0.11 (0.01–0.60)		0.31 (0.03–0.51)	
Major Hepatectomy	1.15 (0.45–2.90)	0.76		
R1 Margin	1.22 (0.46–3.23)	0.17		
Adjuvant Chemotherapy	0.79 (0.32–1.97)	0.62		
Liver to Colon time interval	0.97 (0.73–1.28)	0.84		
Primary Site Right Colon	1	0.52		
Left Colon/Sigma	0.45 (0.07–2.74)	0.88		
Rectum	0.92 (0.20–4.13)	0.46		
Liver resection morbidity	0.92 (0.30–2.77)			
Colorectal resection morbidity	1.53 (0.48–4.84)			
Primary T1	1	0.03	1	0.04
T2	1.56 (1.04–1.75)		0.36 (0.16–1.44)	
T3	2.16 (2.01–2.57)		1.72 (1.21–3.71)	
T4	2.33 (2.02–3.00)		2.21 (1.44–4.32)	
Primary N1	1	0.01	1	0.02
N2	1.00 (0.19–5.28)		1.43 (1.21–2.33)	
N3	7.56 (1.95–29.34)		2.41 (1.44–4.51)	
Steatohepatitis Kleiner score 0/1/2	1	0.36		
Kleiner score 3/4	1.71 (0.11–3.23)			
Kleiner score 5/6/7/8	3.21 (0.01–6.22)			
Fibrosis F0	1	0.98		
F1a	1.19 (0.51–2.79)			
F1b	–			
F1c	1.06 (0.42–2.72)			
F2	0.95 (0.19–4.58)			
Sinusoidal dilation Absent	1	0.17		
Mild	0.47 (0.10–2.20)			
Moderate	2.44 (0.86–6.92)			
Severe	1.44 (0.31–6.69)			
Nodular Regenerative Hyperplasia 1	1	0.29		
2	1.14 (0.32–4.03)			
3	0.21 (0.02–1.64)			
4	2.27 (0.50–10.25)			
Tumor Regression Grade 1	1	0.02	1	0.01
2	1.12 (1.01–2.43)		1.72 (1.23–3.88)	
3	1.26 (1.11–4.12)		2.11 (1.65–3.16)	
4	3.12 (1.21–4.31)		2.98 (1.01–4.31)	
5	3.79 (1.32–5.45)		3.15 (2.13–5.43)	

* Confidence interval.

Table 3
Predictive factors of Disease Free Survival.

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)*	*P* Value	OR (95% CI)	P Value
Female Sex	0.79 (0.44–1.43)	0.45		
Age	1.00 (0.97–1.02)	0.92		
Bilobar Disease	2.78 (1.33–5.81)	0.007	8.66 (1.42–52.88)	0.01
N Lesions	1.06 (0.97–1.16)	0.19		
Size Lesions	1.00 (0.99–1.00)	0.69		
Upfront resectable at diagnosis	0.48 (0.20–1.14)	0.09		
Association of Biological drugs	1.11 (0.60–2.03)	0.73		
Radiotherapy	1.21 (0.65–2.25)	0.53		
CEA	1.00 (0.99–1.00)	0.42		
RECIST Progressive Disease	1	0.03		0.04
Stable Disease	1.41 (0.11–1.43)		0.52 (0.10–2.72)	
Partial Response	0.45 (0.24–0.84)		0.08 (0.007–0.89)	
Major Hepatectomy	0.68 (0.36–1.26)	0.22		
R1 Margin	2.11 (1.13–3.95)	0.01	1.36 (1.08–1.70)	0.02
Adjuvant Chemotherapy	1.02 (0.57–1.82)	0.92		
Liver to Colon time interval	1.00 (0.90–1.13)	0.88		
Primary Site Right Colon	1	0.46		
Left Colon/Sigma	1.06 (0.27–4.17)		1	
Rectum	1.63 (0.50–5.32)			
Liver resection morbidity	1.38 (0.70–2.72)	0.34		
Colorectal resection morbidity	1.29 (0.56–2.97)	0.53		
Primary T1	1	0.53		
T2	1.77 (0.10–29.09)			
T3	1.18 (0.15–8.97)			
T4	1.00 (0.11–9.11)			
Primary N1	1	0.01	1	0.13
N2	1.29 (0.57–2.90)		1.40 (0.31–6.29)	
N3	3.12 (1.04–9.33)		3.40 (0.52–22.23)	
Steatohepatitis Kleiner score 0/1/2	1	0.90		
Kleiner score 3/4	0.96 (0.54–1.71)			
Kleiner score 5/6/7/8	1.45 (0.12–7.19)			
Fibrosis F0	1	0.69		
F1a	0.65 (0.32–1.31)			
F1b	–			
F1c	0.88 (0.26–2.91)			
F2	0.79 (0.27–2.26)			
Sinusoidal dilation Absent	1	0.13		
Mild	2.25 (1.08–4.68)			
Moderate	1.40 (0.66–2.99)			
Severe	0.75 (0.23–2.62)			
Nodular Regenerative Hyperplasia 1	1	0.71		
2	0.62 (0.24–1.61)			
3	1.19 (0.54–2.62)			
4	0.93 (0.28–3.06)			
Tumor Regression Grade 1	1	0.003	1	0.01
2	2.23 (1.12–3.44)		1.87 (1.11–3.83)	
3	2.89 (1.13–4.16)		2.34 (1.89–3.11)	
4	3.01 (2.11–5.89)		3.16 (2.33–4.19)	
5	3.88 (1.99–5.77)		3.21 (2.34–4.12)	

* Confidence interval

in the liver or elsewhere. The patients' survival times were evaluated using Kaplan–Meier curves and were compared with the log-rank test. A backward stepwise Cox regression model was performed to identify prognostic factors influencing OS and DFS.

Statistical analysis was performed using IBM SPSS Statistics for Macintosh (Version 20.0. Armonk, NY: IBM Corp.), and significance was accepted at $p < 0.05$.

Results

Forty-three out of the 62 patients (69.3%) of the study cohort presented with bilobar liver disease, 41 (66.1%) with 3 or more lesions and 27 (43.5%) with at least one lesion 50 mm or larger. Only 12/62 patients (19%) were considered resectable at diagnosis. Patients demographics and type of resections including combined MWA are shown in Table 1.

No patients developed complications related to the primary tumor during neoadjuvant chemotherapy. According to the RECIST criteria, 5 patients (8.1%) were categorized as “Progressive Disease”, 22 (35.5%) as “Stable Disease” and 35 (56.5%) as “Partial Response”.

Of the 35 patients with a radiologic response to neoadjuvant chemotherapy, 29 (82%) also showed histopathologic downstaging. R0 liver resection was recorded in 46 patients (74.2%). One patient had a TRG of 1 (1.6%), 10 (16.1%) had a score of 2, 25 (40.3%) had a score of 3, 24 (38.7%) had a score of 4, and 2 (3.2%) had a score of 5.

No perioperative mortality occurred, and 14 patients (22.6%) experienced complications (12 patients Clavien-Dindo I–II; 2 patients with biliary leak).

Forty-two patients (67.7%) underwent additional systemic therapy, and, after 4 ± 2 months, 47 patients (76%) underwent surgery of the primary tumor (Table 1). No mortality occurred, and 9 patients (19.1%) developed a complication with 4 Clavien-Dindo III–IV (3 anastomotic leaks and 1 acute myocardial infarction).

Forty-seven patients (75.8%) showed recurrence, and 37 of these (78.7%) had liver involvement. Sixteen patients (43.2%) underwent second liver resection.

The median OS of patients was 30 (4–103) months with 1-, 3-, 5-year survival rates of 95%, 76%, and 55%, respectively, while the DFS rates were 47%, 20%, and 16%, respectively.

Multivariate analysis showed that only RECIST criteria ($p = 0.01$), T-stage ($p = 0.04$), N-stage ($p = 0.02$) and TRG (0.01) were independently associated with OS (Table 2).

Regarding DFS, bilobar presentation ($p = 0.01$), RECIST criteria ($p = 0.04$), the R1 margin ($p = 0.02$) and TRG ($p = 0.01$) were significant at multivariate analysis (Table 3).

A subgroup analysis was then performed according to the response to neoadjuvant treatment; patients with a radiologic response had significantly better OS and DFS than patients without (5-y OS: 65% vs. 50%, $p = 0.04$; 5-y DFS: 20% vs. 10%, $p = 0.03$; Fig. 1). Patients with a pathologic response showed a significantly better OS and DFS than those without (5-y OS: 75% vs. 56%, $p = 0.04$; 5-y DFS: 45% vs. 11%, $p = 0.01$; Fig. 2).

Discussion

For patients with synchronous CRLM presenting with symptoms related to the primary, the decision to resect the colorectal cancer is straightforward [33]. However, when the primary tumor is asymptomatic, different management options should be considered. The combined approach is still reserved for minor liver resections and non-complex surgery of the primary, although recent publications are widening indications [18,34,35]. Notwithstanding, if combined resection can be performed, the potential benefits of one surgical procedure over two are clear and should be pursued [36,37].

Several arguments against upfront resection of the primary tumor have been raised: I) morbidity remains an issue (reaching 50%, with 15–30% anastomotic leaks), possibly delaying the treatment of systemic disease that is, the main determinant of a patient's survival [16,35,38,39]; II) in preclinical studies, the primary tumor has been shown to inhibit metastatic growth, suggesting that resection and immunosuppression, could result in a growth stimulus to the liver disease [40,41]; III) a delay in treatment could turn CRLM unresectable, possibly missing the chance of cure; IV) the advances in modern chemotherapy, have been associated with impressive results, suggesting that the rapid administration could be used for downstaging and as a "test-of-time", sparing unnecessary surgery to non-responding patients [15,42–45].

In this setting, LFA seems a promising strategy. As shown by our results, this is the preferred treatment for a high tumor burden in the liver (69% bilobar, 66% more than 3 lesions, 81% unresectable disease) and advanced rectal cancer (74% T3-T4, 61% N+); this is because advanced disease of the liver could benefit from the downstaging effect of systemic therapy and because rectal cancer is still considered a relative contraindication to combined resection [46,47].

No patients developed complications related to the intact primary during systemic therapy, confirming the safety of this strategy and low chance of complications in this timeframe [20,48].

Most patients were categorized having a "Partial Response" after chemotherapy, confirming the downstaging effect of modern regimens [49]. As demonstrated by the high rate of minor hepatectomies performed in our series, upfront systemic treatment could also permit a more conservative surgical approach to the liver, reducing morbidity and enhancing parenchymal sparing surgery, especially in the setting of a chemotherapy-damaged liver [15]. Furthermore, the response to neoadjuvant therapy was an independent factor influencing prognosis, possibly helping in the selection of patients who could benefit from surgery [50]. The importance of chemotherapy is furthermore enhanced by the association with survival of the TRG score [51,52]; The pathologic response could be a surrogate marker of tumor biology, and, although its prognostic value is accepted, no formal studies have been performed in patients undergoing LFA, a protocol in which chemotherapy plays the most important role. It is also true that neoadjuvant chemotherapy induces changes in the normal liver parenchyma possibly increasing the rate of postoperative complications due to liver insufficiency; for this reason, we always aim to a parenchyma preserving strategy during resection. Furthermore, only a 3.2% rate of major complications were shown and no association of survival with steatohepatitis, fibrosis, SOS, or NRH was observed in our series. Another drawback of neoadjuvant systemic treatment is the chance of having "disappearing metastasis" at surgical exploration: it is our policy to refrain from resecting a lesion that is not confirmed during intraoperative ultrasonography in favor of a more conservative surgical strategy as these are advanced patients that will probably recur. Most likely, some of these patients could receive a second hepatectomy in case of liver-only relapse during follow-up.

Seventy-six percent of patients underwent CRC resection, completing all the steps of LFA. Patients who did not complete the protocol had disease progression and excluded from CRC resection [35,53]. The percentage of patients completing all the steps in the classical strategy was reported to be less than 30% [54,55]; therefore, it could be speculated that LFA ultimately leads to a higher chance of offering better survival rates.

In contrast with liver surgery, the percentage of patients experiencing major grade complications following CRC resections was high, (mainly anastomotic leakage), highlighting that this should be considered when deciding the management of patients.

The OS and DFS rates of our case series were comparable to those of the other approaches for synchronous CRLM [23]. However, a high rate of recurrence was seen; patients presenting with synchronous disease of the liver are, per se, considered as having a poor prognosis. In addition, LFA patients normally present with advanced disease of the liver, and this could explain the high recurrence rate. Therefore, an intensive and appropriate surveillance program should be recommended. Notwithstanding, although with a scarce prognosis due to the abovementioned reasons, LFA patients have survival outcomes that are comparable to patients with a lower tumor burden and managed with other approaches [56].

According to Cox regression analysis, well-known oncologic features of cancer patients such as T Stage, N Stage and response after neoadjuvant treatment both at imaging and pathology were demonstrated to be independently associated with OS; this confirms that the biological behavior of the tumor is the main determinant of the patients' oncological outcome and that a surgical strategy should be based on the evaluation of these characteristics.

RECIST criteria and TRG were also independently associated with DFS together with bilobar presentation and R1 resection. Bilobar presentation could jeopardize the opportunity to achieve a negative margin that, in turn, is well known to be associated with recurrence [57]. Therefore, planning the resection should follow the appropriate selection of patients considering liver disease, the response to neoadjuvant treatment as well as the opportunity to achieve an R0 resection, to minimize recurrences [18].

To the best of our knowledge, the evidence concerning LFA available in the literature is negligible. According to the latest meta-analysis, the whole body of evidence was composed of 131 patients described in 4 studies over a time period of 30 years [23]. One of the papers included 58 patients from 250 institutions, showing the strict indication and paucity of evidence [54]. Since then, a few more experiences have been published [58–61]. Because no randomized controlled trials have been published and since the available studies show numerous biases and heterogeneity in terms of tumor characteristics, indications, neoadjuvant treatment protocols, endpoints, and outcome monitoring, the need for further evidence was timely and appropriate.

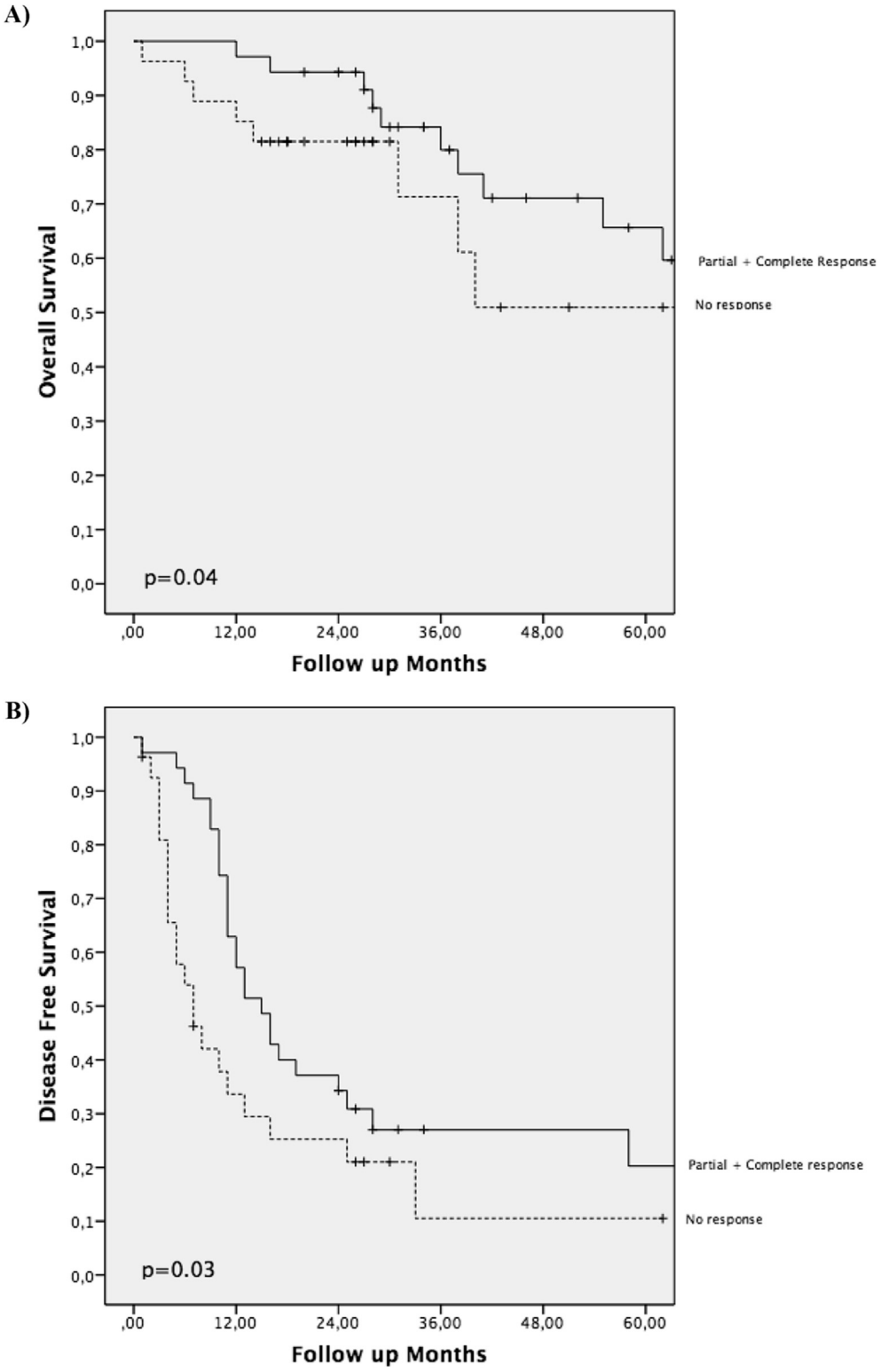

Fig. 1. A) Patient's Overall Survival and B) Disease-Free Survival curves according to radiologic response to chemotherapy.

The main issue for the surgeon remains the selection of patients: we believe that the best patient who could benefit from LFA is the one presenting with an asymptomatic advanced primary tumor located in the rectum needing neoadjuvant treatment, with a low chance of developing complications related to the primary and with a high burden of metastatic disease in the liver. As soon as the downstaging effect of neoadjuvant treatment is noted, liver resection should be carried out [17]. The classic approach should be reserved for patients with limited CRLM who do not require downstaging therapy or when the primary tumor is at risk of developing complications [6].

This study has some limitations, mainly based on the single center, retrospective nature that could have led to selection bias. Notwithstanding, our series is one of the largest available in the

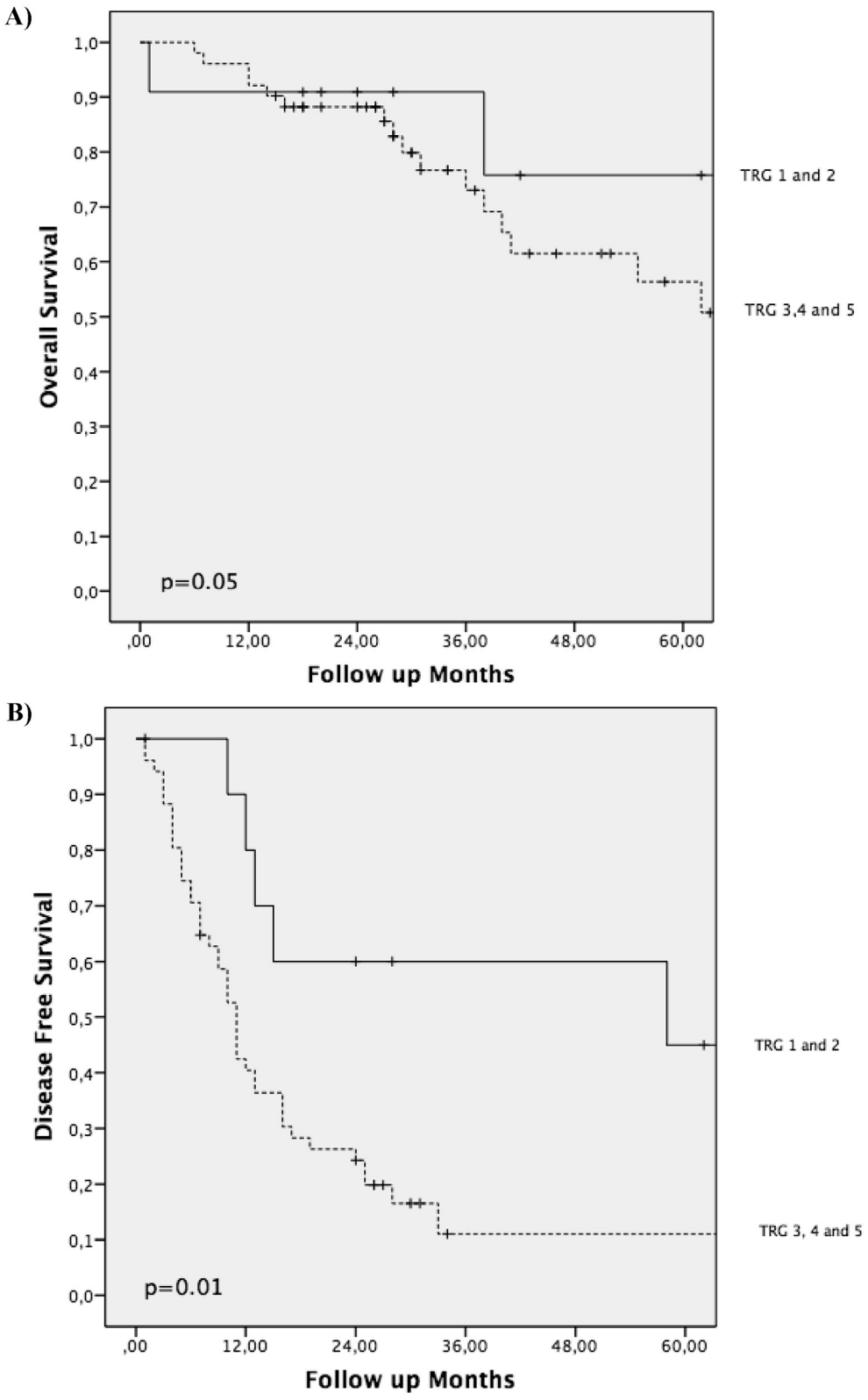

Fig. 2. A) Patient's Overall Survival and B) Disease-Free Survival curves according to pathologic response to chemotherapy.

literature, the first describing response to chemotherapy, pathological characteristics and the one with the longest follow-up, resulting in reliable oncological outcomes.

In conclusion, LFA is a feasible and oncologically safe strategy for the management of synchronous CRLM, with good short- and long-term outcomes. However, a higher level of evidence studies are needed to identify patients who could receive a maximum benefit from this approach. Patient selection is a critical point and should be based on a multidisciplinary and multi-step process at the time of diagnosis, before LFA and subsequent surgery of the

primary to identify predictors outcome eventually improving overall survival.

Conflict of interest statement

No financial disclosures or conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejso.2018.03.008.

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