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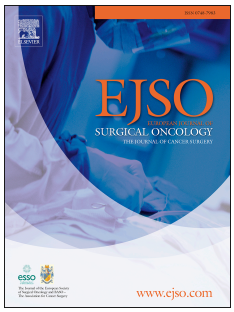

The liver-first approach for locally advanced rectal cancer and synchronous liver metastases

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PII: S0748-7983(18)32029-8

DOI: https://doi.org/10.1016/j.ejso.2018.12.007

Reference: YEJSO 5188

To appear in: *European Journal of Surgical Oncology*

Accepted Date: 8 December 2018

Please cite this article as: Nierop PMH, Verseveld M, Galjart B, Rothbarth J, Nuyttens JJME, van Meerten E, Burger JWA, Grünhagen DJ, Verhoef C, The liver-first approach for locally advanced rectal cancer and synchronous liver metastases, *European Journal of Surgical Oncology* (2019), doi: https://doi.org/10.1016/j.ejso.2018.12.007.

The liver-first approach for locally advanced rectal cancer and synchronous liver metastases.

Shortened title: Liver-first for rectal liver metastases.

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No funding; no disclosures

Abstract

Background

Patients with locally advanced rectal cancer (LARC) and synchronous liver metastases (sRLM) can be treated according to the liver-first approach. This study aimed to evaluate prognostic factors for completing treatment and in how many patients extensive lower pelvic surgery might have been omitted.

Methods

Retrospective analysis of all patients with LARC and sRLM treated at the Erasmus MC Cancer Institute according to the liver-first between 2003 and 2016.

Results

In total 129 consecutive patients were included. In 90 patients (70%) the liver-first was completed. Ten patients had a (near) complete response (ypT0-1N0) of their primary tumour. In 36 out of 39 patients *not* completing the liver-first protocol palliative rectum resection was withheld. Optimal cut-offs for CEA level (53.15 µg/L), size (3.85 cm) and number (4) of RLMs were identified. A preoperative CEA level above 53.15 µg/L was an independent predictor for non-completion of the liver-first protocol (p = 0.005).

Conclusion

Ten patients had a (near) complete response of their primary tumour and, in retrospect, rectum sparing therapies could have been considered. Together with 36 patient in whom palliative rectum resection was not necessary this entails that nearly 40% patients with LARC and sRLM might be spared major pelvic surgery if the liver-first approach is applied. A predictor (CEA) was found for non-completion of the liver-

first protocol. The majority of patients underwent resection of both primary tumour and hepatic metastasis with curative intent. These findings together entail that the liver-first approach may be considered in patients with LARC and sRLM.

INTRODUCTION

The liver-first approach – preoperative systemic chemotherapy followed by hepatic resection for colorectal liver metastases (CRLM) and resection of the primary tumour as last procedure – was first described in 2006. [1] This approach was initially considered for patients with advanced CRLM and a "normal" colorectal carcinoma (e.g. not locally advanced) because extensive metastases could not be treated in one session with the primary tumour. During the same period, our centre advocated the liver first approach for patients with locally advanced rectal cancer (LARC) and synchronous rectal liver metastases (sRLM). [2-4]

Low pelvic surgery after chemoradiotherapy (CRTx) is associated with considerable post-operative complications. This is a reason to treat the sRLM first, because postoperative morbidity of hepatic resections is generally low and patients who then have progressive disease may be spared the high morbidity of low pelvic surgery. Currently, only general prognostic factors and risk scores, such as the Fong criteria [5], are available to predict whether treatment will be completed. These criteria might not be sufficient for patients with LARC and sRLM.

The liver-first approach also gives a good chance of an optimal pre-treatment (i.e. CRTx) of the LARC, hereby maximising the chance of a (near) complete response. These patients could be treated with watchful waiting or other rectum sparing therapies and might only need extensive lower pelvic surgery in case of recurrence of disease.

The aim of the current study was twofold: to evaluate currently available prognostic factors in patients treated for LARC and sRLM according to the liver-first protocol and to evaluate in how many patients extensive lower pelvic surgery might have been omitted when treated according to this approach for LARC and sRLM.

MATERIAL AND METHODS

This is a retrospective analysis of a prospectively maintained patient database, consisting of all patients who underwent resection for RLM in a tertiary referral centre in the Netherlands. The database comprises of multiple perioperative and clinicopathological characteristics of both primary rectal cancer and RLM. The current study was approved by the medical ethics committee of the Erasmus University Medical Centre Rotterdam (MEC-2018-1031).

Patients and treatment approach

Since 2003 all patients presented at our centre with LARC and sRLM are treated according to the liver-first approach. All consecutive patients between 2003 and 2016 were included in the current study. LARC was defined as tumour >5 cm, expected distance of <2 mm to mesorectal fascia or ingrowth of adjacent organ (T4) on MRI or lymph node positive tumour meaning 1 lymph node >8 mm or 4 lymph nodes > 5 mm on CT scan or MRI). Patients described in previous publications by this group were also included in the study. [2, 4] Treatment for all patients was assessed in a multidisciplinary team (MDT). After systemic treatment with chemotherapy radiological tumour response was assessed. If no disease-progression was observed, laparotomy and liver resection were performed first. After liver surgery, neoadjuvant (C)RTx was administered after consultation again by the MDT. After finishing (C)RTx, patients were re-staged by CT Thorax/Abdomen and low pelvic MRI. Surgery of the primary tumour was performed as last stage. Surgery was planned 6-10 weeks after neoadjuvant (C)RTx. [6] Complications were categorised according to the Clavien-Dindo classification. [7]

Pre-operative chemotherapy

CT-scan of thorax and abdomen and CEA levels assessed the response to pre-operative chemotherapy after two or three cycles. Response was defined as decrease in tumour size and CEA levels. In patients

scheduled for resection, the interval between the last course of chemotherapy and liver surgery was at least four weeks. Bevacizumab was excluded from the last course of chemotherapy to ensure that the interval between the last course of bevacizumab and surgery was at least six weeks.

Liver resection

The pathological response was categorized as complete response (CR) when no vital tumour cells were found, as partial response (PR) when both vital tumour cells and treatment effects were found and as stable disease (SD) when merely vital tumour cell and no treatment effect was observed.

Statistical analysis

Categorical data are presented as absolute numbers and percentages. Continuous data are presented as medians (and interquartile ranges (IQR)) or means (with standard deviations (SD)). Different proportions between groups were tested using the Chi-squared test. Medians were compared using the Mann-Whitney U test. The Kaplan-Meier method was used to estimate survival. Follow-up was estimated using the reverse Kaplan-Meier method. Overall survival (OS) was considered the time between the date of resection of the sRLM and the date of death. Patients were censored when alive at last follow-up date. Uni- and multivariable binary logistic regression analysis was performed to evaluate prognostic factors for the completion of the liver-first protocol and Odds Ratios (OR) for these factors were calculated. All variables with p-values below 0.05 on univariable analysis were included in the multivariable analysis. Receiver operating characteristic (ROC) analysis was used to identify the optimal cut-off points of the continuous variables (preoperative CEA, number and size of sRLM). The area under the curve (AUC) was used to determine the discriminatory performance of the logistic regression model. P values below 0.05 were considered significant. All analyses were performed using SPSS (SPSS version 24.0, Inc., IBM Corporation, Chicago, Ill., USA) and R version 3.5.1 (http://www.r-project.org).

RESULTS

There were 152 patients with LARC and sRLM treated at our centre during the study period. In principle, all patients with LARC and sRLM, who are referred to our centre are treated according to the liver-first protocol since 2003. However, over the years there have been some exceptions. We identified 23 patients with LARC and sRLM who were not treated according to the liver-first protocol. The reasons for these exceptions are listed in figure 1.

In total, 129 patients with LARC and sRLM were treated according to the liver-first protocol and included in the current study. Baseline characteristics are displayed in table 1. A flowchart of the clinical course of these 129 patients is presented in figure 1.

Pre-operative chemotherapy and response of the liver metastases

In accordance with the liver-first protocol, all 129 patients received pre-operative chemotherapy (median 4 cycles (IQR: 3-6)). Patients predominantly received capox (N= 104, 81%). Other treatment regimens included folfox (N=13, 10%), folfiri (N= 7, 8%), capecitabine (N= 2, 2%), irinotecan (N=2, 2%) and folfirinox (N= 1, 1%). Of one patient the type of chemotherapy was unknown. In 34 patients (26%) bevacizumab was added to the regimen. After chemotherapeutic treatment 5 patients (4%) had a complete radiological response, while 102 patients (79%) had responded partially and 20 patients (16%) had stable disease. Two patients (2%) had growth of their metastases despite systemic treatment, but were treated surgically nonetheless.

Surgical treatment and pathological response of the RLM

In total 117 of the 129 patients were treated surgically for RLM. In twelve patients (9%) RLMs were not resected due to intra-operatively discovered unexpected progression of metastatic disease. Of the 129 patients that underwent laparotomy for intended surgical treatment of sRLM 121 (94%) had no or only mild complications (Clavien-Dindo grade 0-2) and 8 patients (6%) had severe complications (Clavien-Dindo grade >2), of whom one patient (1%) died postoperatively. Histopathological evaluation of the liver tumours showed pathological PR in 84 patients (72%), CR in 12 patients (10%) and SD in 5 patients (5%). In 15 patients (13%) there was no pathological response evaluation available, due to treatment with ablative therapy only (N= 5) or it was not reported in the pathology reports (N= 10).

Rectal cancer

In 39 of the 129 patients (30%) the liver first protocol could not be completed. As stated, twelve patients did not undergo liver resection. In five patients sRLM were resected, but did not start with (C)RTx due to progressive metastatic disease or interim death. In the remaining 22 patients, 21 revealed progressive metastatic disease at restaging between liver and rectal surgery and one of them died before rectal surgery. In these 21 patients the median time between liver resection and restaging that revealed progressive metastatic disease was 3 months (IQR: 3.0-4.5). The treatment given regarding their primary tumour is displayed in table 2.

In 90 patients (70%) surgery of the rectum with curative intent was performed and the liver-first protocol was completed. Of these 90 patients, 78 (87%) did not experience any signs of obstruction that needed additional procedures. In eleven patients (12%) there was the need for a colostomy (5 prior to and 6 during the liver-first protocol) and in one patients (1%) a rectal stent was placed. Of the 90 patients that completed the treatment trajectory 77 (86%) had no or only mild complications (Clavien-Dindo grade 0-2) and 13 patients (14%) had severe complications (Clavien-Dindo grade >2), but no postoperative

mortality was observed. Nine patients (10%) had a pathological complete response of the primary tumour and one patient had an ypT1N0 tumour.

Follow-up and survival

Median follow-up of survivors was 58 months (IQR: (30 – 86 months)). Median OS of the complete intention to treat group was 35 months (IQR: 18 – 92 months). Median OS in the 90 patients that completed the liver-first protocol was not reached at five years. For the 39 patients that did not complete the liver-first protocol the median OS was 14 months (IQR: 8 – 19 months). The Kaplan-Meier curves are presented in figure 2.

Prognostic factors for non-completion of the liver-first protocol

No significant association between any of the tested variables and not completing the liver-first protocol was found. ROC analysis identified the optimal cut-offs for preoperative CEA (53.15 μg/L), size (3.85 cm) and number (4) of RLMs. The use of optimal cut-offs slightly improved performance of the logistic regression model, as the AUC increased from 0.699 to 0.713. The improved logistic regression model showed that patients with CEA levels above 53.15 μg/L have a higher odds for not-completion of the liver-first protocol (OR: 3.482; p = 0.005)). Results of the logistic regression analyses are presented in table 3. However, seventeen patients out of the 36 patients with a CEA level of >53.15 μg/L still completed the treatment sequence.

DISCUSSION

The current study presents the results of the largest series of patients treated for rectal cancer and sRLM according to the liver-first protocol to date. New cut-off threshold for several well-known risk factors that improve prognostication in patients with sRLM were identified. Most importantly, it demonstrated that in 92% (36 out of 39) of the patients not completing the liver-first protocol extensive pelvic surgery was eventually not necessary. Another ten patients had responded so well to the preoperative CTx and (C)RTx (ypT0N0 N= 9 and ypT1N0 N= 1) that rectum preservation could have been an option. This adds up to 36% (46 out of 129 patients) of the total group in whom omission of extensive rectal surgery could have been considered.

Patients with LARC and rRLM are at high risk of disease progression and futile extensive pelvic surgery. Therefore, the liver-first approach could be the optimal approach in patients with sRLM, especially as it increases the possibilities for rectum sparing strategies. TAMIS or watchful waiting could be considered if a clinical (near) complete response is seen, as it is oncological safe to preserve the rectum in selected cases. However, should TAMIS be performed and if histopathology reveals a >ypT1N0 tumour, local and systemic recurrence is lurking and completing major excision is recommended. [8-14] Several studies have shown that pelvic surgery for rectal cancer is associated with high morbidity rates, resulting in long-term complications. [15, 16] However, in these studies stage IV patients are being disregarded. By applying the LF approach pre-eminently those patients are selected out who will not have any survival advantage from major surgery and can therefore be saved from this kind of surgery. Therefore, it is remarkable that nearly all attention for rectum sparing therapies goes out to patients with stage I and II (sometimes stage III) rectal cancer, since these patients experience relatively good oncological outcome and survival rates. [11, 13, 17, 18]

The majority (70%) of patients treated according to this protocol can be treated with curative intent. Similar results have been shown in multiple other studies. [1, 2, 4, 19] Recently, it was acknowledged by

an intention-to-treat analysis, that no differences in completion rate between the classical approaches and the liver-first approach are observed, showing that up to 35% of patients does not complete the full treatment trajectory irrespective of the chosen treatment approach. [20] In addition, no differences have been demonstrated in the literature between the three treatment sequences (liver-first, bowel-first or synchronous resection) in terms of OS, disease free survival or postoperative complication rates. [19, 21-25] However, no randomised controlled trial comparing the three sequences has been performed and therefore the currently available literature might subject to selection bias.

As stated, in this and other series describing the liver-first approach, approximately 30-40% of patients do not complete the full liver-first treatment protocol. [1, 2, 4, 19, 26] In order to define in which patients local treatment, rather than palliative chemotherapy is desirable, this study evaluated prognostic factors for completion of the liver-first protocol. With regard to prognosis in patients with colorectal liver metastases several risk scores have been proposed [5, 27-29], of which the Fong score is mostly utilized. [5] The current study shows that the generally used risk factors have limited prognostic value for completion of the liver-first protocol, as the AUC only reached up to 0.699. When optimizing the cut-off values of continuous variables the AUC increases to 0.713, which still indicates only moderate discriminatory ability. In this study one significant prognostic variable with regard to completion of the protocol was found, namely CEA levels above 53.15 µg/L. This might be useful in counselling patients, yet cannot be used to withhold therapy according the liver first protocol as seventeen patients out of the 36 patients with a CEA level of >53.15 µg/L still completed the treatment sequence. No literature is available specifically describing prognostic factors for the non-completion of the treatment sequence in patients treated for synchronous RLM, therefore external validation of the results of this study is warranted. Also further research is needed to identify new biomarkers that can improve patient stratification and selection before starting the liver-first protocol.

A proportion of incurable patients with the primary tumour in situ require additional surgical treatment nonetheless, due to obstruction, perforation or pain. [30, 31] In this study, three patients not completing the liver-first protocol ultimately underwent rectum excision. In addition, systemic chemotherapy induces rapid symptom relief in patients with high-risk rectal cancer. [32] This, combined with the fact that most patients in the current study did not need a surgical intervention, implies that it is relatively safe not to resect the primary rectal tumour. A recent systematic review and a meta-analysis comparing non-resection and resection in patients with unresectable stage IV CRC show similar complication and symptom rates in both groups, which validates the currently obtained results. [30, 31] The systematic reviews failed to find a survival benefit. [30, 33] However, in contrast, a meta-analysis [31] and a nationwide population-based study did. [34] It seems as if there will only be certainty about whether or not the resection of the primary tumour is beneficial for overall survival in the case of unresectable metastases when the results of an ongoing randomised controlled trial (CAIRO 4) will be published. [35] Considering the fact that symptom rates are comparable between resected and non-resected patients and a survival benefit, if any, remains to be proven, the liver-first protocol is a reasonable approach in patients with synchronous RLM and rectal cancer.

This study has several limitations that should be acknowledged. This is a retrospective analysis of selected patients in a single institution. It should also be taken into account that some patients start the liver-first protocol, but have evident progression under chemotherapy and are therefore excluded from liver surgery, as limited yield should be expected from surgical treatment in case of disease progression during chemotherapeutic treatment.[36] Since the currently used database consists of patients who underwent laparotomy for intended surgical treatment of sRLM, patients that stopped the liver-first protocol before resection of the RLMs were not included in this study. Therefore, it should be given consideration that a small proportion of patients that initially started the liver first protocol was not included in the analysis, which could have affected the results obtained.

CONCLUSION

The current study has shown that in this series over one-third of patients could be spared from extensive lower pelvic surgery. In patients not completing the liver-first protocol extensive pelvic surgery was ultimately was not necessary in 92% of the cases and a substantial proportion of patients could have been candidates for rectal preserving therapies. Although a predictor for the non-completion of the liver-first protocol was found, this cannot be used to exclude patients from the liver first protocol as the majority of patients underwent resection of both the primary tumour and the hepatic metastasis with curative intent. These findings together entail that the liver-first approach may be considered in patients with LARC and sRLM.

Legend

Figure 1. Flowchart of the clinical course of the 129 patients

Figure 2: Kaplan-Meier graphs for OS

Table 1: Baseline characteristics of patients treated by the liver first protocol

Table 2. Primary tumour not resected curatively

Table 3: Results of the logistic regression analyses

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Table 1. Preoperative baseline characteristics

		Total (N=129)	Completed LF (N=90, 70%)	Not completed LF (N=39, 30%)	P-value
Gender	Male	92 (71.3%)	69 (76.7%)	23 (59.0%)	0.041*
	Female	37 (28.7%)	21 (23.3%)	16 (41.0%)	
Age	Median (IQR)	62 (56-68)	63 (56-69)	62 (56-67)	0.565
ASA	ASA I-II	116 (89.9%)	78 (86.7%)	38 (97.4%)	0.062
	ASA > II	13 (10.1%)	12 (13.3%)	1 (2.6%)	
RLM characteristics					
Number of RLM	1 tumour	25 (19.4%)	17 (18.9%)	8 (20.5%)	0.830
	>1 tumour	104 (80.6%)	73 (81.1%)	31 (79.5%)	
Size of largest RLM	≤ 5 cm	106 (82.2%)	79 (87.8%)	27 (69.2%)	0.011*
	>5 cm	23 (17.8%)	11 (12.2%)	12 (30.8%)	
Preoperative CEA	≤ 200 µg/L	112 (91.1%)	81 (95.3%)	31 (81.6%)	0.014*
	>200 µg/L	11 (8.9%)	4 (4.7%)	7 (18.4%)	
	Missing	*6 patients*			
Bilobar metastasis	No	112 (91.1%)	81 (95.3%)	31 (81.6%)	0.018*
	Yes	11 (8.9%)	4 (4.7%)	7 (18.4%)	
EHD known preoperatively	No	110 (85.3%)	79 (87.8%)	31 (79.5%)	0.222
	Yes	19 (14.7%)	11 (12.2%)	8 (20.5%)	

LF = liver first protocol; IQR = interquartile range; ASA = American society of anaesthesiologists; Physical Status Classification System; RLM = rectal liver metastases; CEA = Carcinoembryonic antigen; EHD = extrahepatic disease; * = significant p-value

Table 2. Treatment for primary tumour if not resected curatively

	N=39 (%)
Palliative rectum resection	3 (7.7%)
Palliative (C)RTx and colostomy	9 (23.1%)
Colostomy	2 (5.1%)
Palliative (C)RTx	13 (33.3%)
Rectal stenting	1 (2.6%)
None or palliative CTx and/or pain medication only	10 (25.6%)
Died post hepatectomy	1 (2.6%)

(C)RTx = (chemo)radiotherapy; CTx= chemotherapy

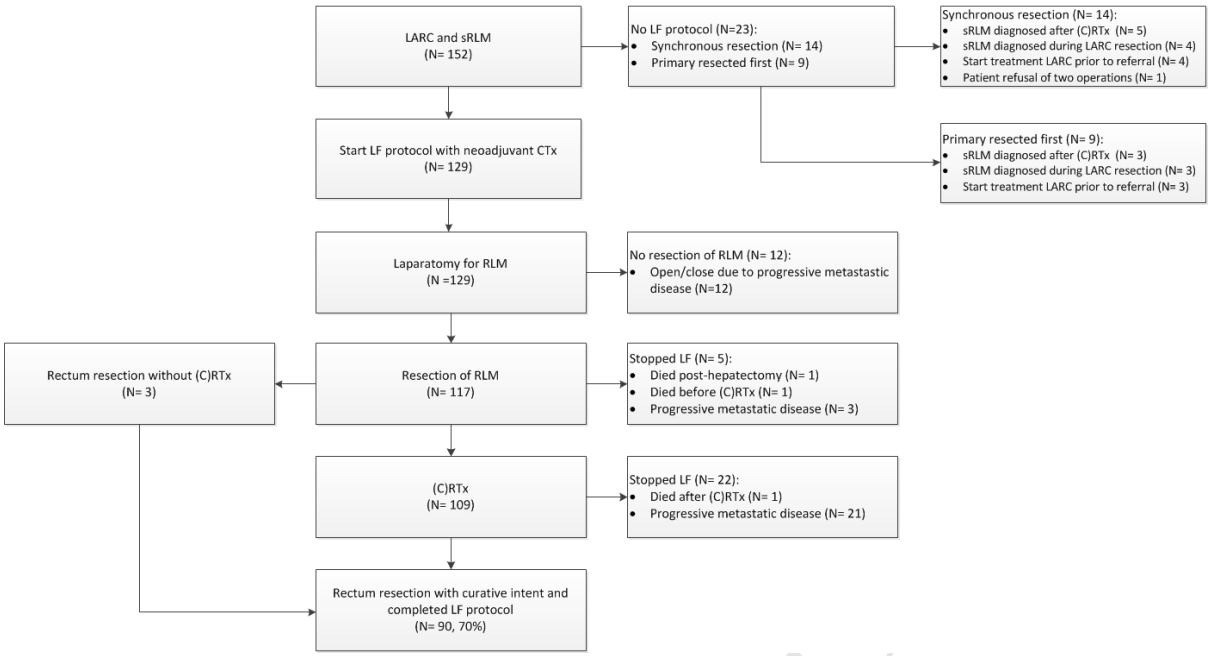
Table 3. Uni- and multivariable binary logistic regression analysis for the non-completion of LF

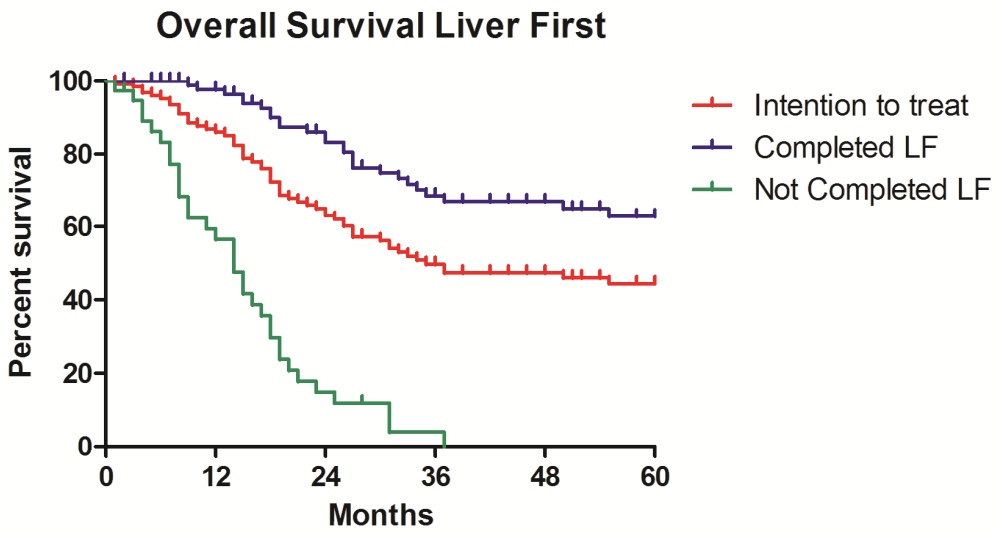
Variables	Univariable		Multivariable	
	OR [95% CI]	P-value	OR [95% CI]	P-value
Male gender	0.438 [0.196-0.977]	0.044*	0.524 [0.216-1.271]	0.153
Age (cont.)	1.009 [0.971-1.048]	0.657		
ASA > II	0.171 [0.021-1.364]	0.096		
Number of RLM >1	0.902 [0.353-2.309]	0.830		
Size of metastasis >5 cm	3.192 [1.263-8.070]	0.014*	2.456 [0.917-6.578]	0.074
CEA > 200	4.573 [1.251-16.717]	0.022*	3.742 [0.968-14.464]	0.056
Bilobar RLM	1.883 [0.849-4.175]	0.120		
Pre-operative EHD	1.853 [0.681-5.043]	0.227		

Improved uni- and multivariable binary logistic regression analysis for the non-completion of LF

Variables	Univariable		Multivariable	
	OR [95% CI]	P-value	OR [95% CI]	P-value
Male gender	0.438 [0.196-0.977]	0.044*	0.481 [0.194-1.190]	0.113
Age (cont.)	1.009 [0.971-1.048]	0.657		
ASA > II	0.171 [0.021-1.364]	0.096		
Number of RLM >4	1.625 [0.751-3.518]	0.218		
Size of metastasis >3.85 cm	2.251 [1.021-4.962]	0.044*	1.470 [0.593-3.642]	0.405
CEA > 53.15	4.000 [1.746-9.162]	0.001*	3.482 [1.451-8.372]	0.005*
Bilobar RLM	1.883 [0.849-4.175]	0.120		
Pre-operative EHD	1.853 [0.681-5.043]	0.227		

LF= liver first protocol; OR = odds ratio; ASA= American society of anesthesiologists; CRLM= colorectal liver metastases; CEA= carcinoembryonic antigen; EHD = extra hepatic disease; * = significant p-value





No. at risk						
Intention to treat	129	101	67	44	35	28
Completed LF	90	81	62	43	35	28
Not compl. LF	39	20	5	1	0	0

Conflicts of Interest Statement

Manuscript title: ***Optimizing prognostication in patients with synchronous liver metastases from locally advanced rectal cancer treated according to the liver-first approach.***

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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