

ORIGINAL ARTICLE

Liver-first strategy for synchronous colorectal liver metastases – an intention-to-treat analysis

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Abstract

Background: The liver-first strategy signifies resection of liver metastases before the primary colorectal cancer. The aim of the present study was to compare failure to complete intended treatment and survival in liver-first and classical strategies.

Methods: All patients with colorectal cancer and synchronous liver metastases planned for sequential radical surgery in a single institution between 2011 and 2015 were included.

Results: A total of 109 patients were presented to a multidisciplinary team conference (MDT) with un-resected colorectal cancer and synchronous liver metastases. Seventy-five patients were planned as liver-first, whereas 34 were recommended the classical strategy. Twenty-six patients (35%) failed to complete treatment in the liver-first group compared to 10 patients in the classical group ($P = 0.664$). Reason for failure was most commonly disease progression.

A total of 91 patients had the primary tumor resected before the liver metastases of which 67 before referral and 24 after allocation at MDT. Median survival after diagnosis in this group was 60 (48–73) months compared to 46 (31–60) months in the group operated with liver-first strategy ($n = 49$), ($P = 0.310$).

Discussion: Up to 35% of patients with colorectal cancer and synchronous liver metastases do not complete the intended treatment of liver and bowel resections, irrespective of treatment strategy.

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Introduction

Liver metastases are present in 15–25% of patients with colorectal cancer at the time for diagnosis of the primary,^{1,2} defined here as synchronous liver metastases. Treatment for potential cure includes surgical resection of all tumor sites. However, due to comorbidity or extensive disease only a minority of patients are candidates for curative resections. When surgical treatment is indicated, different strategies can be utilized. In the classical strategy the primary is resected first followed by resection of the liver metastases at a second stage with perioperative chemotherapy. More recently, simultaneous resection of the primary and the liver lesions has been employed, mainly for limited liver disease without the need for major liver resections.³ A third option is preoperative chemotherapy, followed by resection of the liver metastases and resection of the bowel primary at a

second stage.⁴ This liver-first strategy has the potential advantage of allowing resection of advanced liver disease in patients when the primary tumor is asymptomatic. No clear advantage or disadvantage with either of the three strategies in terms of survival has been demonstrated.⁵

Most previous studies evaluating the liver-first strategy only include liver resected patients.^{6–9} There are thus scarce data on how many and why patients scheduled for the liver-first strategy do not complete both liver and bowel resections, which is the aim of the present study to investigate.

Methods

The medical records of all patients with colorectal liver metastases between 2011 and August 2015 presenting to a

multidisciplinary team conference (MDT) were scrutinized and patients with synchronous liver metastases were chosen for further analysis. All patients had biopsy proven adenocarcinoma of colorectal origin. Patients were staged with multidetector computed tomography (MDCT) of the chest and multiphase MDCT of the abdomen. Magnetic resonance imaging (MRI) of the liver with liver-specific contrast was selectively used. In patients with rectal cancer, MRI of the pelvis was used for staging. From these patients, only patients with asymptomatic primary, resectable hepatic metastases (with or without the need for portal vein embolization) and, when present, resectable extrahepatic metastases were selected and thus constitute the patient cohort of the intention to-treat analysis. Data were retrospectively extracted from patient records and patients were divided into groups according to treatment strategy chosen, that is, classical or liver-first strategy. Patients in whom a simultaneous strategy was recommended were excluded.

In the intention to-treat analysis, only patients referred with their primary un-resected are included. Survival and recurrence free survival analysis, comparing the liver-first and classical strategies also include patients presented to the liver MDT after bowel resection, irrespective if the primary was symptomatic or not. After completed resections, patients had follow-up with MDCT of the chest and abdomen every six months the first two years and then yearly up to five years.

The study protocol was approved by the regional ethics committee.

Table 1 Characteristics of patients presenting with un-resected colorectal primary cancer and synchronous liver metastases

	Liver-first strategy	Classical strategy	P
Number of patients	75	34	
Male gender	56 (75%)	17	0.016
Age (years)	65 (58–72)	67 (58–70)	0.649
Current smoking	10 (13%)	5	1.000
Diabetes mellitus	4 (5%)	4	0.436
ASA 3	20 (27%)	5	0.208
Body mass index (kg/m ²)	25 (23–27)	24 (22–26)	0.136
Rectal primary	47 (63%)	15	0.095
CEA at diagnosis (µg/L)	17 (5–100)	9 (4–40)	0.106
Clinical T stage 4	24 (32%)	18	0.090
Clinical node positive	57 (76%)	25	0.449
Number of liver tumors	3 (2–4)	2 (1–4)	0.016
Size of largest liver tumor (mm)	25 (20–48)	22 (14–30)	0.039
Patients with lung metastases	10 (13%)	4	1.000

Data are presented as number (percentage) or median (interquartile range). ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen.

Statistics

Results are expressed as median (interquartile range). Mann–Whitney *U* test was used to compare continuous data and Fischer's exact test for categorical data. Kaplan–Meier was used to estimate recurrence-free and overall survival from time of cancer diagnosis and the log-rank test was used to compare between liver-first and classical strategies. Cox regression analysis was used to calculate hazard ratios and 95% confidence intervals for risk factors for recurrence-free and overall survival. Factors with a *P*-value < 0.1 on univariable regression were included in a multivariable analysis. A *P* < 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 22 (IBM, Armonk, NY, USA).

Results

A total of 176 patients with resectable synchronous liver metastases were identified and included in the study. Of these, 67 had their primary tumor resected before referral, giving 109 patients presenting to a MDT with radiologically resectable synchronous liver metastases and un-resected primary colorectal cancer. Seventy out of 109 patients (64%) were staged with MRI of the liver with gadoteric acid contrast. Two patients scheduled for simultaneous resection were excluded.

Characteristics for patients chosen for the liver-first or classical strategy are shown in Table 1.

Of the 75 patients chosen for the liver-first approach, 26 (35%) failed the treatment plan (Table 2). Reasons for failure of the

Table 2 Liver-first strategy failure and completed

	Failure	Completed	P
Number of patients	26	49	
Male gender	18	38	0.578
Age (years)	70 (60–74)	65 (58–69)	0.083
ASA 3	7	14	0.796
Body mass index (kg/m ²)	25 (23–27)	25 (23–28)	0.467
Rectal primary	13	34	0.133
CEA at diagnosis (µg/L)	12 (4–134)	18 (6–96)	0.700
Clinical T stage 4	10	14	0.440
Clinical node positive	20	37	1.000
Number of liver tumors	4 (2–7)	2 (2–4)	0.017
Size of largest liver tumor (mm)	28 (20–56)	25 (20–45)	0.789
Patients with lung metastases	3	7	1.000
MRI for liver staging	17	31	1.000
Resectable in liver at first MDT	20	40	0.763
Chemotherapy as first treatment	22	47	0.494

Data are presented as number or median (interquartile range). ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen; MRI, magnetic resonance imaging; MDT, multidisciplinary team conference.

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