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Surgical Management of Synchronous Colorectal Liver Metastases: A Multicenter Study Comparing Classic, Combined and Reverse Strategy

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Abstract: Optimal management sequence for the primary tumor and the liver in synchronous colorectal liver metastases (SCLM) is still controversial. Except reviews, studies comparing the 3 surgical approaches are infrequent. The present study aimed to describe the surgical management of patients operated of SCLM. In particular, we compared short-term outcomes and survival according to the surgical strategy. A multicentric retrospective study was conducted on 125 patients with SCLM. Surgical strategy was defined as classic (colorectal first approach), combined and reverse (liver-first approach). Between 2008 and 2013, 87 patients completed the classic strategy, 24 combined strategy and 14 reverse strategy. The 3 groups were comparable regarding pre-operative data. Liver metastases involvement was significantly higher in reverse group. Severe cumulative postoperative morbidity was 39.2%, similar between the 3 strategies. Ninety-day mortality was higher in combined group (12.5%, p>0.05). Failure rate of liver first approach was 17%. The 3-year overall survival (OS) was 73% in classic group, 78% in combined group and 93% in reverse group. The 3-year disease free survival (DFS) was 29%, 30% and 19% for classic, combined and reverse strategy respectively. There was no significant difference with regard to OS and DFS between 3 groups. We demonstrated that liver first approach is safe and feasible with acceptable perioperative and survival outcomes despite initially worse prognostic criteria. Reverse strategy can be applied to a vast majority of patients independently to the liver tumor burden and should be considered progressively as a reference in the management of SCLM.

Keywords: Synchronous colorectal liver metastases, comparative study, reverse strategy, liver-first approach.

INTRODUCTION

Colorectal cancer is the third most common cancer in Europe. Twenty to twenty five percents of patients have ~~a~~ stage IV disease at diagnostic. Liver is the first organ involved and synchronous colorectal liver metastases (SCLM) are present in 15-25 % of cases [1,2]. For an optimal clinical management, especially the choice of a surgical strategy, only synchronously CLM (detected at or before the diagnosis of the primary tumor) should be considered. Complete surgical resection is the only chance for long-term survival. Approximately 80 % of patients present with unresectable liver metastases at diagnosis [2,3] and for those who are inoperable , 5-year survival rate is only 4-9 % [2]. Recently, with advances in chemotherapy and improvement of operative techniques, the 5-years survival of resected patients has risen to 40-58 % [4]. For some selected patients, cure can be achieved after conversion chemotherapy even for initially unresectable CLM.

The optimal management of SCLM is still controversial, including chemotherapy, surgery, radiotherapy and locoregional therapies. Defining the best treatment sequence is difficult because there are multiple possible combinations between an important number of treatment modalities and 2 target organs. The classic surgical strategy consists of primary tumor resection followed by chemotherapy with the aim of removing liver metastases at a second stage. Apart from a natural selection of patients with a less favorable disease, the rationale is that the primary tumor is the

source of liver metastases and potential complications. Good outcomes following simultaneous resection of colorectal neoplasm and liver metastases were reported in case of easily resectable SCLM. Considering that SCLM drive the prognosis, the liver-first strategy was proposed (reverse strategy). This strategy was developed to prevent delays in chemotherapy and to control liver metastases first, optimizing the chance of potentially curative resection in case of advance metastatic disease [5].

The optimal management sequence for the primary tumor and liver metastasis in SCLM is still controversial. Except for retrospective reviews [4], studies comparing the 3 surgical approaches are infrequent, especially multicenter studies or studies that focuses only on rectal cancer. The present study aimed to describe the surgical management of patients operated for SCLM. In particular we compared short-term outcomes and survival according to the surgical strategy.

METHODS

Patients and definition

A multi-institutional retrospective database from 3 French tertiary hepato-biliary centers was established on patients scheduled for curative liver resection of SCLM between January 2008 and December 2013. The study was performed in accordance with the precepts established by the Helsinki declaration. Patients with SCLM diagnosed during or after primary surgery were excluded. The computerized medical records of selected patients were queried for data on clinicopathologic factors, including *RAS* mutation status, treatment variables, perioperative details, pathologic response and survival. Fong clinical risk score was used to determine liver tumor burden [6].

Regarding liver resection, R0 margin was defined by a tumor-free margin ≥ 1mm [7]. Histological response was evaluated using Blazer classification, defined as complete response when there were no residual tumor cells, major response when tumor cells accounted for 1-49 % of residual cells and minor response when tumor cells accounted for more than 50 % of residual cells [8].

Preoperative management and surgical procedure

Before surgery, all patients underwent a physical examination, laboratory evaluation and imaging studies, including computed tomography scan of chest, abdomen and pelvis. SCLM were deemed resectable when a hepatectomy could achieve a negative margin while preserving more than 30 % of the total estimated liver volume, sparing 2 continuous liver segments, and maintaining vascular inflow/outflow and biliary drainages [9]. In patients with an anticipated insufficient future liver remnant, preoperative portal vein embolization and staged hepatectomy were proposed.

Based on patient medical and oncological history, preoperative and postoperative chemotherapy were proposed during multidisciplinary tumor board meeting. Neoadjuvant chemotherapy referred to chemotherapy before any surgical time (colorectal for classic strategy or liver surgery in case of reverse strategy), interval chemotherapy referred to chemotherapy between colorectal and liver surgery. Adjuvant chemotherapy referred to any chemotherapy after the latest surgical procedure.

Surgical treatment strategy was defined as classic (colorectal primary tumor resection before liver resection), combined (colorectal and liver resection during the same operation, without two-stage hepatectomy) and reverse (liver resection first, before colorectal resection). Liver resections were performed only with curative R0 intent. Intraoperative ultrasonography was routinely used. Ablative therapies were used for deep SCLM when safe liver resection was not possible. Resectable and controlled extrahepatic disease was not an absolute contraindication to liver resection.

For patients with peritoneal metastasis (PM), extent of PM was staged according to the Peritoneal Cancer Index (PCI). The cytoreductive surgery (CRS) was graded with the completeness of cytoreduction score (CC-score) [10]. Hyperthermic intraperitoneal chemotherapy (HIPEC) was performed using close abdomen technique using oxaliplatin (360 mg/m^2 delivered over 30 minutes at 42°C, plus systemic 5-fluorouracil) or mitomycin C (30 mg/m^2 delivered over 60 minutes at 42°C).

Postoperative morbidity and mortality

Postoperative morbidity and mortality were recorded at 30- and 90-day, and graded with Dindo classification [11]. Bile leak was defined and graded according to the International Study Group for Liver Surgery (ISLGS) definition but without measuring bilirubin level in drain [12]. Grade A bile leakage does not change patient clinical management. Grade B bile leakage requires active therapeutic intervention but is manageable without relaparotomy, whereas in grade C, relaparotomy is required. Post-hepatectomy haemorrhage (PHH) was also defined and classified using ISGLS classification [13]. Transfusion of up to 2 units of packed red blood cells (PRBC) is considered as being grade A PHH. Grade B PHH requires transfusion of more than 2 units of PRBC, whereas the need for invasive re-intervention such as embolization and/or re-laparotomy defines grade C. Liver failure was defined by "50-50 Criteria" (prothrombin time < 50 % and serum bilirubin level > 50 µmol/L on post-operative day 5) [14]. Cut surface abscess (without evidence of bile during and after the drainage) and pneumonia/pleural

effusion were also reported. Cumulative morbidity was defined by at least one complication during colorectal or liver resection.

STATISTICAL ANALYSIS

Descriptive results were expressed as number (percentage) for qualitative variables or by mean ± standard deviation (SD) or median (minimum-maximum) for quantitatives. Comparisons between the 3 groups were performed using Chi^2 test (or Fisher exact test when conditions for Chi^2 were not fulfilled) for qualitatives and by analysis of variance (ANOVA, or Kruskal-Wallis test in case of non-normality) for quantitatives.

Overall survival (OS) was defined as the time from the diagnostic to the date of death, the date of last follow up, whichever came first. Disease-free survival (DFS) was defined as time from diagnostic until recurrence or last follow-up. Deceased patients were censored at the date of death. Median survival times and survival rates were computed using Kaplan-Meier method.

RESULTS

Patient and tumor characteristics

Between January 2008 and December 2013, 125 patients were operated for SCLM in 3 centers. Eighty-seven patients (69.6 %) completed a classic strategy, 24 (19.2 %) a combined and 14 (11.2 %) a reverse strategy. The 3 groups were similar with regard to demographic data, primary tumor characteristics and extra hepatic disease (Table 1). Except for threatening location, SCLM were significantly more numerous in the reverse strategy group (Table 1).

Medical oncologic approach

Neoadjuvant chemotherapy (CT) and targeted therapy were significantly more frequent in reverse strategy (Annex 1). Median number of CT cycle was 5 (2-16), without significant differences in the three groups. Oxaliplatin was the most common CT administered (51.8%). Among the 21 patients with extraperitoneal rectal tumor, 80.1 % received neoadjuvant rectal radiotherapy (100 % in reverse group). Ninety eight percent of patients received interval CT, with a median number of 5 cycles and a delay after surgery of 42 days, without significant differences in classic and reverse groups. Adjuvant CT was administered in 76.8 % of patients. Median number of cure was 6 (2-15), with a median delay after surgery of 56 days (17-138) without difference between group (Annex 1).

Resection of primary tumor and outcomes

Laparoscopic resection was done in 22.4 % of cases. Among 19 patients with bowel obstruction, upfront resection, fecal diversion and colonic stent were performed in 11, 6 and 2 cases respectively without significant difference in the 3 groups (Annex 2). Anastomotic leakage was reported in 10.4 % of patients (Table 2). Severe morbidity reached 14.2 % in classic group *vs* 7.1 % in reverse group (not significant, Table 2).

Surgical management of liver metastases and outcomes

Forty-six patients had major hepatectomy. Two-stage hepatectomy was performed in 17.6 % and portal venous embolization in 18.4 %. Eight patients had a laparoscopic resection. Operative characteristics were summarized in table 2. Severe morbidity reached 35.7 % in reverse group *vs*. 27.6 % in classic group (not significant, Annex 2). R0 resection was performed in 76.7 % and 61.9 % of patients in the first and second stage respectively, without significant difference in groups (Annex 3-4). Complete pathologic response was 8.7% for the entire series, a higher percentage was observed in the reverse group (21.4 %) without any statistically significant difference. There was no difference in the median percentage of residual cancer cells. Chemotherapy-induced liver injury was present in 55.2 % of patients (Annex 3-4).

Feasibility of reverse strategy

Initially 17 patients were scheduled for the reverse strategy. Three patients (17 %) needed an emergency primary tumor resection before liver surgery for bowel obstruction. Fourteen patients (83 %) completed the scheduled treatment plan. Two (14.3 %) had an early liver recurrence and necessitated an unexpected liver resection during the primary tumor surgery. All patients were able to receive adjuvant chemotherapy. Second-line chemotherapy was administered in 7 patients, in 4 for poorly tolerated side effects from the first line and in the last 3 for disease progression between two-staged hepatectomy.

Extrahepatic disease

Retroperitoneal lymph nodes involvement was initially suspected in 5 patients. Three had node-picking resection and 2 had extensive retroperitoneal lymph node dissection. No patient had histological involvement.

Lung metastasis was suspected in 13 patients. Nine had lung recurrence and only 1 was confined to the lung. Among 13 patients, 2 were operated and both presented pulmonary relapse.

Six patients had CRS+HIPEC for synchronous peritoneal carcinomatosis. The median PCI was 4 (range 2-17) and median number of SCLM was 4.5 (range 3-14). After CRS, all patients had CC-0 score. Five patients had CRS+HIPEC associated with liver resection. Major hepatectomy was performed in 2 cases (right and left lobectomy). One patient had CRS+HIPEC during reverse strategy. Ninety-days mortality was 0 % and 1 patient developed a severe

complication (bile leak). Disease recurrence was observed in 4 patients, localized only in the liver.

Survival and cumulative outcomes

Mean follow-up from the date of the diagnostic was 37.7 months (+/- 18.1 months). The 3-years OS was 73 % for classic group, 78 % for combined group and 93 % for reverse group (Figure 1). The 3-years DFS was 29 %, 30 % and 19 % for classic, combined and reverse group respectively (Figure 1). There was no significant difference in OS and DFS between the 3 groups. Liver was the site of recurrence in 83.3 % of relapses. There was no significant difference between the 3 strategies with regard to severe cumulative postoperative morbidity (Table 2). Ninety-day mortality was 6.9 % in classic group, 12.5 % in combined group and 0 % in reverse group without significant difference (Table 2).

Table-1: Preoperative characteristics of 125 patients with synchronous colorectal liver metastases, who completed classic, combined or reversed strategy

Characteristics	Patients (n=125)	Surgical Strategy			p-value
		Classic (n=87)	Combined (n=24)	Reverse (n=14)	
General					
Age, y, median (range)	62 (23-84)	62 (26-83)	64 (23-84)	61 (44-79)	ns
Gender, M/F	84/41	60/27	18/6	6/8	ns
ASA Score ≥ 3, n (%)	23 (18.4)	12 (13.8)	7 (29.2)	4 (28.6)	ns
CEA plasma level, ng/mL, (sd)	147.3 (479.8)	171.8 (562.3)	57.6 (126.2)	192.9 (415.6)	ns
Ki-*RAS* mutation, n (%)	28 (33.7)	22 (37.3)	4 (26.7)	2 (22.2)	ns
Primary tumor					
Location, n (%)					ns
Colon and upper rectum	104 (83.2)	77 (88.5)	16 (66.7)	11 (78.6)	
Medium and lower rectum	21 (16.8)	10 (11.5)	8 (33.3)	3 (21.4)	
pTNM, n (%)					ns
pT3-pT4	117 (93.6)	83 (95.4)	22 (91.7)	12 (85.7)	
N+	87 (69.6)	61 (70.1)	19 (79.8)	7 (50)	
Symptomatic, n (%)	97 (77.6)	68 (78.2)	18 (75)	11 (78.6)	ns
Abscess, perforation	6 (4.8)	6(6.9)	0 (0)	0 (0)	
Anemia (Hb < 80 g/L or transfusion)	8 (6.4)	4 (4.6)	4 (16.7)	0 (0)	
Bowel obstruction	19 (15.2)	13 (14.9)	5 (20.8)	1 (7.1)	
Liver metastases					
Median, n (range)	3 (1-17)	3 (1-17)	1 (1-5)	6.5 (3-13)	<0.001
Largest metastase, mm, (sd)	36.5 (23.2)	37.0 (23.3)	26.3 (13.2)	50.9 (28.8)	0.012
Bilateral distribution, n (%)	61 (48.8)	42 (48.3)	6 (25)	13 (92.9)	0.003
Fong score ≥ 3, n (%)	74 (59.2)	55 (63.2)	9 (37.5)	10 (71.4)	0.047
Resectability class one, n (%)	97 (77.6)	65 (74.7)	23 (95.8)	9 (64.3)	0.040
Threatening location, n (%) *	96 (76.8)	65 (74.7)	17 (70.8)	14 (100)	ns
Suspected extra hepatic disease, n (%)	24 (19.2)	19 (21.8)	2 (8.3)	3 (21.4)	ns
Lung	13 (10.4)	11 (12.6)	1 (4.2)	1 (7.1)	
Peritoneal metastasis	6 (4.8)	4 (4.6)	1 (4.2)	1 (7.1)	
Retroperitoneal lymph nodes	5 (4.0)	4 (4.6)	0 (0)	1 (7.1)	

ASA: American Society Anesthesiologists, CEA: Carcinoembryonic Antigen. *Threatening location was defined by a size < 20mm, hilar or sushepatic contact. sd: standard deviation, ns: non-significant.

Morbidity was scored according to Dindo-Clavien classification, except for Bile leak and hemorrhage classified according to International Study Group for Liver Surgery (ISGLS) classification. *Cumulative outcomes referred to colorectal and liver resection morbimortality. Concerning combined group, only specific or cumulative morbidity was reported to avoid any mistake of classification between colorectal- or liver-related complications. ns: non-significant; nc: no comparison was performed.

Table-2: Outcomes of primary tumor resection and liver metastases surgery

Variables	Patients (n=125)	Surgical Strategy			p-value
		Classic (n=87)	Combined (n=24)	Reverse (n=14)	
CUMULATIVE OUTCOMES, n (%) *					
Morbidity	69 (55.2)	47 (54.0)	13 (54.2)	9 (64.3)	ns
Clavien ≥ 3	49 (39.2)	33 (37.9)	10 (41.7)	6 (42.9)	ns
Mortality					
30-days mortality	6 (4.8)	4 (4.6)	2 (8.3)	0 (0)	ns
90-days mortality	9 (7.2)	6 (6.9)	3 (12.5)	0 (0)	ns
MORBIDITY OF COLORECTAL RESECTION, n (%)					
Morbidity	-	20 (23.0)	-	3 (21.4)	nc
Clavien ≥3	-	13 (14.9)	-	1 (7.1)	nc
Specific surgical complication,					
Anastomotic leakage	13 (10.4)	9 (10.3)	3 (12.5)	1 (7.1)	ns
Clavien ≥3	10 (8.0)	7 (8.0)	2 (8.3)	1 (7.1)	ns
Intraperitoneal abscess	4 (3.2)	3 (3.4)	0 (0)	1 (7.1)	ns
Clavien ≥3	2 (1.6)	2 (2.3)	0 (0)	0 (0)	ns
Haemorrhage	2 (1.6)	2 (2.3)	0 (0)	0 (0)	ns
Clavien ≥3	1 (0.8)	1 (1.1)	0 (0)	0 (0)	ns
MORBIDITY OF LIVER RESECTION, n (%)					
Morbidity	-	33 (37.9)	-	6 (42.9)	nc
Clavien≥3	-	24 (27.6)	-	5 (35.7)	nc
Specific surgical complications					
Bile leak (ISGLS)	17 (13.6)	13 (14.9)	2 (8.3)	2 (14.3)	ns
Grade A	2 (1.6)	2 (2.3)	0 (0)	0 (0)	ns
Grade B	15 (12.0)	11 (12.6)	2 (8.3)	2 (14.3)	ns
Grade C	0 (0)	0 (0)	0 (0)	0 (0)	ns
Haemorrhage (ISGLS)	13 (10.4)	10 (11.5)	1 (4.2)	2 (14.2)	ns
Grade A	1 (0.8)	1 (1.1)	0 (0)	0 (0)	ns
Grade B	4 (3.2)	3 (3.4)	1 (4.2)	0 (0)	ns
Grade C	8 (6.4)	6 (6.9)	0 (0)	2 (14.2)	ns
Liver Failure (50/50)	19 (15.2)	15 (17.2)	4 (16.7)	0 (0)	ns
Cut end abscess	7 (5.6)	4 (4.6)	2 (8.3)	1 (7.1)	ns
Pneumonia / Pleural effusion	13 (10.4)	7 (8.0)	3 (12.5)	3 (21.4)	ns

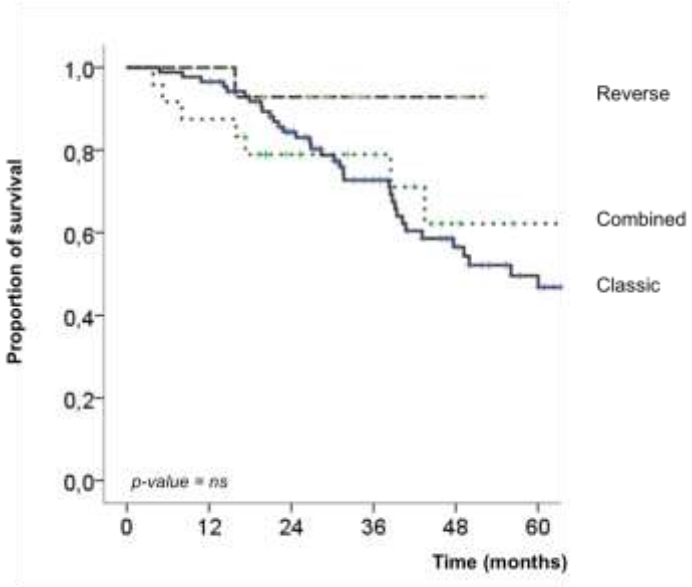

Figure 1A: Overall survival

Fig-1: Overall survival (1A OS) and disease free survival (1B DFS) of 125 patients who completed classic, combined or reverse surgery

At risk (months)	0	12	24	36	48	60
Classic, n	87	84	64	44	27	18
Combined, n	24	21	14	11	5	3
Reverse, n	14	14	12	4	3	0

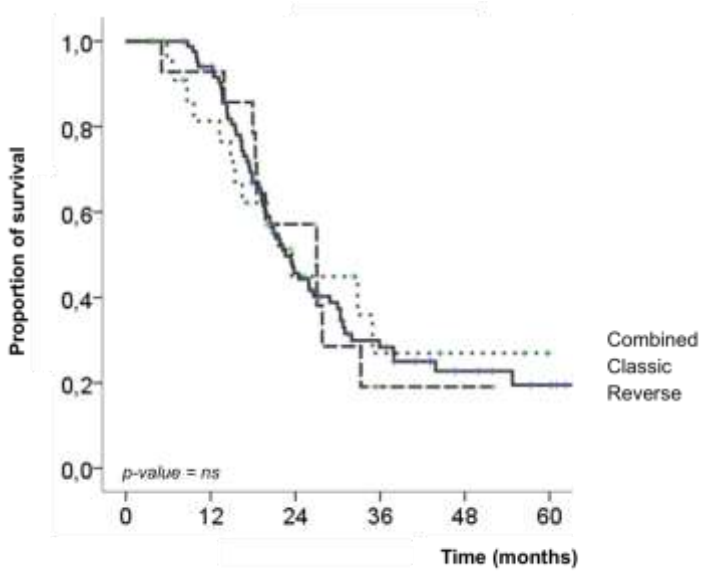

Figure 1B: Disease-free survival

At risk (months)	0	12	24	36	48	60
Classic, n	85	78	34	18	9	5
Combined, n	24	17	7	3	2	0
Reverse, n	14	13	7	1	1	0

Supporting Information

Annex 1

Medical management of 125 patients with synchronous liver metastases, who completed classic, combined or reverse strategy.

Annex 2

Operative management of primary tumor and liver metastases

Annex 3

Postoperative histological data of 125 patients who completed colorectal and liver resections

Annex 4

Cause of postoperative deaths

SUPPORTING INFORMATION

Annex-1: Medical management of 125 patients with synchronous liver metastases, who completed classic, combined or reverse strategy

Variables	Patients (n = 125)	Surgical Strategy			p-value
		Classic (n = 87)	Combined (n = 24)	Reverse (n = 14)	
Neoadjuvant chemotherapy (CT), n (%)	56 (44.8)	24 (27.6)	18 (75)	14 (100)	< 0.001
Median number of cycles, n (range)	5 (2-16)	4 (2-14)	5 (3-15)	6 (4-16)	ns
Median time between CT and surgery, days (range)	27 (1-77)	30 (1-57)	29 (1-77)	22 (13-43)	ns
First line regiment, n (%)					0.024
Oxaliplatin based	29 (51.8)	12 (50)	10 (55.6)	7 (50)	
Irinotecan based	13 (23.2)	6 (25)	5 (27.8)	2 (14.3)	
Oxaliplatin and Irinotecan based	6 (10.7)	1 (4.2)	0 (0)	5 (35.7)	
Second line chemotherapy, n (%)	9 (16.1)	4 (16.7)	3 (16.7)	2 (14.3)	ns
Reason of the change, n (%)					ns
tumor progression	5 (55.6)	2 (50)	3 (100)	0 (0)	
side effect	4 (44.4)	2 (50)	0 (0)	2 (100)	
Targeted therapy, n (%)	28 (22.4)	10 (11.5)	9 (37.5)	9 (64.3)	< 0.001
Median number of cycle, n (range)	4,5 (2-15)	4 (2-14)	4 (3-14)	6 (3-15)	ns
Neoadjuvant rectal radiotherapy (RT), n (%)*	17 (81.0)	9 (90.0)	5 (62.5)	3 (100)	ns
Median time between RT and rectal surgery, days	43 (8-382)	41 (8-57)	48 (10-61)	122 (43-382)	0.020
Adjuvant chemotherapy (CT), n (%)	96 (76.8)	69 (79.3)	19 (79.2)	8 (57.1)	ns
Median number of cycles, n (range)	6 (2-15)	6 (2-13)	8 (4-15)	4 (2-9)	<0.001
Median time between surgery and CT, days (range)	56 (17-138)	55 (25-138)	63 (17-90)	57 (36-71)	ns
First line regiment, n (%)					ns
Oxaliplatin based	41 (43.2)	25 (36.2)	13 (68.4)	3 (42.9)	
Irinotecan based	41 (43.2)	34 (49.3)	5 (26.3)	2 (28.6)	
Oxaliplatin and Irinotecan based	5 (5.3)	3 (4.3)	1 (5.3)	1 (14.3)	
Second line chemotherapy, n (%)	14 (14.7)	9 (13)	4 (21.1)	1 (14.3)	ns
Reason of the change, n (%)					ns
tumor progression	5 (35.7)	3 (33.3)	2 (50)	0 (0)	
side effect	9 (64.3)	6 (66.7)	2 (50)	1 (100)	
Targeted therapy, n (%)	49 (39.2)	39 (44.8)	6 (25)	4 (28.6)	ns
Median number of cycle, n (range)	6 (0-15)	6 (0-11)	7 (4-15)	4 (2-7)	ns

Neoadjuvant chemotherapy was defined by chemotherapy before colorectal, hepatic surgery or both depending surgical strategy and adjuvant chemotherapy after any surgical time. Targeted therapy included bevacizumab, cetuximab or panitumumab therapy. * Among 21 patients with infraperitoneal rectal tumor. NS: non-significant.

Annex-2: Operative management of primary tumor and liver metastases

Variables	Patients (n = 125)	Surgical Strategy			p-value
		Classic (n = 87)	Combined (n = 24)	Reverse (n = 14)	
PRIMARY TUMOR, n (%)					
Laparoscopic resection	28 (22.4)	20 (23)	4 (16.7)	4 (28.6)	ns
Treatment of bowel obstruction	19 (15.2)	13 (14.9)	5 (20.8)	1 (7.1)	ns
Colonic stent	2 (1.6)	1 (1.1)	1 (4.2)	0 (0)	
Stoma	6 (4.8)	2 (2.3)	3 (12.5)	1 (7.1)	
Up front tumor resection	11 (8.8)	10 (11.5)	1 (4.2)	0 (0)	
With minor stage of 2-stages hepatectomy	13 (10.4)	12 (13.8)	-	1 (7.1)	ns
Fecal diversion / Stoma					
Temporary	37 (29.6)	20 (23.0)	13 (54.2)	4 (28.6)	0.012
Definitive	8 (6.4)	7 (8.0)	0 (0)	1 (7.1)	ns
LIVER METASTASES					
Major hepatectomy, n (%)	46 (36.8)	33 (37.9)	6 (25)	7 (50)	nc
Two-stage hepatectomy, n (%)	22 (17.6)	17 (19.5)	0 (0)	5 (35.7)	nc
Median interval between 2 stages, days (range)	124 (72-360)	136 (72-360)	-	109 (80-239)	nc
Laparoscopic resection, n (%)	8 (6.4)	5 (5.7)	3 (12.5)	0 (0)	nc
Anatomic resections, n (%)	77 (61.6)	57 (65.5)	9 (37.5)	11 (78.6)	nc
Median nb of resected segments /patient (range)	4 (1-6)	4 (1-6)	4 (1-5)	4 (1-5)	nc
Wedge resections, n (%)	85 (68.0)	56 (64.4)	17 (70.8)	12 (85.7)	nc
Median nb of wedge resections/patient (range)	1 (1-12)	1 (1-12)	1 (1-4)	3.5 (1-7)	nc
Focal destructions, n (%)	45 (36.0)	31 (35.6)	4 (16.7)	10 (71.4)	nc
Median nb of focal destruction/patient	2 (1-5)	2 (1-5)	1 (1-2)	2 (1-5)	nc
Portal vein embolization (PVE), n (%)	23 (18.4)	17 (19.5)	1 (4.2)	5 (35.7)	nc
Median delay before hepatectomy, day (range)	58 (32-345)	45 (32-345)	64 (64)	74 (41-173)	nc
Total pedicle occlusion, n (%)	29 (23.2)	27 (31)	0 (0)	2 (14.3)	nc
Median duration of occlusion, min (range)	32 (6-66)	30 (6-66)	0 (0)	45 (45)	nc
Median operative blood loss, mL (range)	350 (0-2550)	360 (0-2550)	200 (0-900)	525 (50-1500)	nc
Red blood cell (RBC) transfusion, n (%)	34 (27.2)	24 (27.6)	6 (25.0)	4 (28.6)	nc
Median nb of RBC transfused, n (range)	2 (1-10)	2.5 (1-10)	2 (1-5)	2.5 (1-6)	nc
Intraoperative metastases discovery, n (%)	24 (19.2)	18 (20.7)	2 (8.3)	4 (28.6)	nc
Pedicle Lymphadenectomy, n (%)	28 (22.4)	23 (26.4)	3 (12.5)	2 (14.3)	nc
Positive lymph nodes, n (%)	5 (4.0)	3 (3.4)	2 (8.3)	0 (0)	nc

Major hepatectomy referred to liver resection ≥ 3 segments. ns: non-significant. nc: no comparison was performed.

Annex-3: Postoperative histological data of 125 patients who completed colorectal and liver resections

Variables	Patients (n = 125)	Surgical Strategy			p-value
		Classic (n = 87)	Combined (n = 24)	Reverse (n = 14)	
SURGICAL MARGIN, n (%)					
Colorectal primary R0 resection	123 (98.4)	86 (98.9)	23 (95.8)	14 (100)	ns
Liver metastases resection					
First-stage hepatectomy, R0	89 (76.7)	60 (74.1)	19 (90.5)	10 (71.4)	ns
Second-stage hepatectomy, R0	13 (61.9)	10 (62.5)	-	3 (60)	ns
HISTOLOGICAL RESPONSE, n (%)*					
Blazer classification					ns
Complete response	10 (8.7)	5 (6)	2 (11.1)	3 (21.4)	
Major response	51 (44.3)	40 (48.2)	6 (33.3)	5 (35.7)	
Minor response	52 (45.2)	36 (43.4)	10 (55.6)	6 (42.9)	
Median % of residual cancer cells, n (range)	49.0 (0-100)	49.0 (0-100)	55.0 (0-90)	40.0 (0-80)	ns
CHEMOTHERAPY-INDUCED LIVER INJURY, n (%)	64 (55.2)	42 (50)	14 (77.8)	8 (57.1)	ns
Steatosis	51 (79.7)	32 (76.2)	14 (100)	5 (62.5)	
Sinusoisal obstruction syndrome (SOS)	8 (12.5)	7 (16.7)	0 (0)	1 (12.5)	
Both	5 (7.8)	3 (7.1)	0 (0)	2 (25)	

Complete response was defined by no residual cancer cells, major response defined by 1% to 49% residual cancer cells remaining, minor response by ≥ 50% cancer cells remaining and no response by 100% cancer cells remaining. For liver resection, R0 resection was defined by a margin ≥ 1mm. * Among 99 patients (exclusion missing data and ablative treatment).

Annex 4: Cause of postoperative deaths

Patient	Strategy	Surgery	POD	Cause of death
1	Combined	Right hepatectomy + Right colectomy	20	Myocardial infarction Septic shock (pneumonitis) -> mesenteric infarction
2	Combined	Right hepatectomy + Right colectomy	18	Septic shock (ascitis infection) Liver insufficiency Portal vein and SHV thrombosis
3	Combined	Focal destruction + Right colectomy	57	Cardiogenic shock / pulmonary embolism
4	Classic	Right hepatectomy + Stoma closure	68	Liver insufficiency Septic shock / Anastomotic leak
5	Classic	Left lateral sectionectomy + Segmentectomy 8 + wedge resection and focal destructions	18	Pulmonary embolism (SHV and IVC thrombosis) Mesenteric infarction
6	Classic	Right hepatectomy + Wedge resection / PVE	3	Budd Chiari (SHV twist) Liver insufficiency
7	Classic	Right trisectionectomy + Wedge resection / PVE	44	Liver insufficiency / Portal vein thrombosis Hepatorenal syndrome - Septic shock
8	Classic	Wedges resections	89	Tumoral progression
9	Classic	Right hepatectomy (2^{nd} stage) + Wedge / PVE	49	Right hepatic artery embolization Septic shock (infection and necrosis of segment IV) Liver insufficiency associated

POD: Postoperative day of death. SHV: Sushepatic vein, IVC: Inferior vena cava. PVE: when portal venous embolization was performed before liver resection. Concerning patients with liver insufficiency, 4 had steatosis and 1 had sinusoidal obstruction syndrome.

DISCUSSION

This study confirmed promising results of reverse strategy in the management of SCLM. In fact, no significant differences in OS and DFS were found between the 3 surgical strategies whereas reverse approach was proposed to patients with significantly higher liver tumor burden. These findings raise the possibility that liver-first strategy could enhance survival of patients who benefit from this strategy, without increasing post-operative complications. Several arguments suggest that reverse strategy could gradually become a gold standard of management of SCLM.

Firstly, the main advantage of reverse strategy is early surgical control of the location that is most likely the cause of patient's death for stage IV colorectal cancer [5]. By treating the SCLM first, this strategy limits delay of chemotherapy due to primary surgery morbidity and could prevent the risk of transformation into non resectable SCLM in case of progression after colorectal resection. Postoperative complications after primary tumor removal in metastatic patients occurred in 23 % [15] and we found in our study 8 % of severe anastomotic leakage. Negative impact of this morbidity on the oncological prognosis was clearly stressed [16] and was explained not only by the delay in chemotherapy but by immunomodulation induced by surgery and infection [17]. Moreover, reverse approach is particularly appealing in rectal cancer. This location presents not only a high morbidity rate but requires radiochemotherapy (RCT). To decrease local recurrence and to improve tolerance, RCT should be performed before rectal resection [18]. Yet, this local therapy is not effective toward SCLM and delay surgical management of the metastatic disease. By treating the hepatic disease first, reverse strategy is focusing on controlling the liver progression to allow an optimal time frame for the treatment of the primary tumor.

Secondly, concerning the management of the primary tumor, neoadjuvant chemotherapy is also effective on colorectal cancer. The efficiency is measurable on the clinical symptoms modification and on the histological response. In advanced rectal tumors, symptoms mildly improved after one or two chemotherapy cycles and a complete histological response was reported in 9.1 % of patients after reverse strategy [19]. Similar results were described in colon cancer. Consequently, the reverse approach appears feasible for colon and rectal cancer, even in case of advanced or symptomatic tumors. Furthermore, the risk of primary tumor progression under chemotherapy appears low, estimated between 7-14 % [20]. We reported here a failure rate of 17 %. Bowel obstruction represents 80 % of primary tumor complications [21] and could be managed with a diverting ostomy without changing the planned surgical strategy. Only perforation or major intestinal hemorrhage should be considered as a contraindication to the liver first approach.

Thirdly, the reverse approach is a chemotherapy first approach. Considering SCLM as a systemic disease, it allows for an immediate and effective systemic treatment of both sites, particularly the SCLM [5]. This concept of chemotherapy first approach is often mandatory because patients included in studies present an important liver tumor burden that requires conversion chemotherapy. However, there are 3 major pitfalls that can be anticipated when using a close monitoring for patients to determine the optimal window of resectability. There is the risk of progression under chemotherapy, the possibility of missing metastases and post-hepatectomy complications. The risk of progression is relatively low (7 %) in patients with resectable disease [22] and can be managed with a second-line of chemotherapy. It could also reflect an aggressive tumor biology that could hardly be controlled by surgery. The risk of missing a metastases is around 46 % for lesions ≤20 mm (23). It exposes patients to a high level of recurrence because less than 20 % of missed lesions present a complete and durable histological response [24]. Nevertheless, they can be managed by fiducial placement, ultrasound-guided resection or adjuvant intra-arterial hepatic chemotherapy. Lastly, chemotherapy induced hepatotoxicity renders surgery more difficult but can be limited by a close monitoring of treatment duration. A regular radiological evaluation has to be performed every 4 to 6 cycles and surgery has to be planned as soon as hepatic disease becomes resectable. In fact, extended chemotherapy does not increase histological response but increases postoperative complications [25].

Our study has several limitations mostly due to the retrospective nature of this work. The small number of patients included in the reverse strategy group could reflect a stronger patient selection and then limit the statistical power of the study. The period of inclusion is short, explaining the small number of cases but also ensuing homogeneity of disease's management. Obviously, the same bias is currently found in other series, with a proportion of reverse strategy varying from 2.8 % to 35 %. Feasibility of classical strategy was impossible to evaluate because of referral selection bias for liver surgery. For combined resections, we were confronted to classification difficulty for the origin of the postoperative morbidity, hepatic or colorectal surgery. Because of this difficulty, cumulative morbidity appears more adapted. Lastly, our DFS is relatively short, reflecting the aggressive behavior of SCLM and inclusion of patients with suspected extra hepatic disease.

CONCLUSION

Considering the reverse strategy as an appealing approach to treat quickly the metastatic

disease we proposed here the third comparative study between classical, combined and reverse strategy in colorectal cancer with SCLM. We demonstrated that liver first approach is safe and feasible with acceptable perioperative and survival outcomes despite initially worse prognostic criteria. Reverse strategy can be applied to a vast majority of patients independently to the liver tumor burden and should be considered progressively as a reference in the management of SCLM.

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