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Oncological strategies for middle and low rectal cancer with synchronous liver metastases☆

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HIGHLIGHTS

- Three different oncological strategies can be applied.
- No one of the oncological strategy seems to be superior for survival.
- The strategy should be adapted to each situation.

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ABSTRACT

Purposes: : In rectal cancer, the incidence of synchronous liver metastases (SLM) ranges from 14% to 30%. The treatment of SLM combines neo-adjuvant chemo- and/or radiotherapy with of one three surgical resection strategies (rectal resection first, liver resection first or simultaneous resection). The present study evaluated the success rate for each resection strategy.
Methods: From January 2005 to December 2013, we retrospectively included all patients with distal (middle and low) rectal cancer (MLRC) and SLM and who had been operated on with curative intent. The primary study endpoint was the proportion of complete resections at both tumour sites. The secondary endpoints were postoperative morbidity, the long-term outcome and risk factors for incomplete resection.
Results: 52 patients were included. There were no significant intergroup differences in the incidence of complete resection (respectively 74%, 66% and 50% in the rectum-first (n = 20), simultaneous (n = 10) and liver-first groups (n = 5); p = 0.3), the overall complication rate or mortality rate after rectal resection (p = 0.5) or liver resection (p = 0.8), overall survival (60, 47 and 38 months, respectively; p = 0.4) or disease-free survival (31, 32 and 7.8 months, respectively; p = 0.1). Emergency surgery was the only risk factor for treatment failure (p = 0.01).
Conclusion: There were no differences in short and long-term outcomes between the three strategies. No one oncological strategy should be favoured for all cases of MLRC with SLM. The strategy should be choosen, based on the oncological emergency (rectum-first or liver-first), predictive factors for morbidity in rectal surgery and MDT discussion.

1. Introduction

In rectal cancer, the incidence of synchronous liver metastases (SLM) ranges from 14% to 30% [1,2]. Treatment of SLM associated with middle or lower rectal cancer (MLRC) is complex because the neoadjuvant therapy differs as a function of the lesion site. Chemoradiotherapy has become the standard treatment for locally advanced rectal cancer. In contrast, perioperative chemotherapy

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has become the standard treatment for colorectal liver metastases [3]. The choice of the best oncological strategy is a critical aspect of patient care.

A conventional, staged, rectum-first strategy was long used to avoid primary tumour complications (such as obstruction and perforation). Simultaneous resection was introduced after the risk of liver metastasis progression had been noted [4–6]. Recently, a "liver-first" strategy (also referred to as the "reverse strategy") has been introduced [7] (especially for advanced liver metastases of colorectal cancer). The rationale behind the "liver-first" strategy is that (i) the patient's prognosis is primarily related to his/her liver status and (ii) rectal resection is associated with a greater risk of complications, which would delay treatment of the SLM [8].

Despite the importance of these specific issues, only three series have compared the three strategies [6,9,10]. Another series specifically assessed MLRC but did not compare the three oncological strategies [11]. Moreover, there are no data on the reasons for treatment failure in MLRC patients as a function of the oncological strategy. This information is essential for increasing the R0 resection rate and thus personalizing and improving the level of care for these patients.

Hence, the primary objective of the present study was to compare the respective success rates (i.e. complete resection) for the three above-mentioned oncological strategies and to identify any predictive factors for successful treatment.

2. Patients and methods

2.1. Inclusion criteria and definitions

From January 2005 to December 2013, we included all MLRC patients with SLM discovered during rectal cancer assessment and who were treated with curative intent. Only metastases discovered before the initiation of any treatment were taken into account. Middle or lower rectal cancer was defined as a tumour located below the Douglas pouch and no more than 7 cm from the internal anal sphincter. Early rectal cancer was defined as T1/T2, N0, whereas locally advanced MLRC was defined as T3/T4 and/or N+. Primary tumours were staged after a digital rectal examination, colonoscopy, endorectal ultrasound imaging and magnetic resonance imaging [12]. A computed tomography (CT) scan of the chest, abdomen and pelvis was performed for metastatic disease staging. Synchronous liver metastases were diagnosed on the CT scan if the lesions were typical. For atypical lesions, combined positron emission tomography/CT or a biopsy was prescribed [13]. Synchronous liver metastases were classified as a function of their resectability. A class 1 resection was defined as resection of less than 4 segments and the presence of a liver remnant of more than 40%. A class 2 resection was defined as resection of 4 or more segments and the presence of a liver remnant of less than 40%. The SLM were classified as initially non-resectable if two or more portal pedicles were involved, if a portal pedicle and a contralateral hepatic vein were involved or if all hepatic veins were involved [14,15]. Patients receiving palliative care (non-operable patients and patients with non-resectable extrahepatic metastases, such as bone and multiple lung metastases, diffuse peritoneal carcinomatosis, etc.) or those with undeniably unresectable SLM (multiple, bilobar metastases or the invasion of major liver vessels) [16] [17] or upper rectum cancer (7–12 cm from the anal verge) were excluded.

2.2. Study design and patient selection

This was a single-centre, retrospective study. From January 2005 to December 2013, patients were retrospectively included on the basis of a prospectively completed multidisciplinary team meeting form. Patients having undergone at least one surgical procedure ($n = 52$) were divided into three groups as a functional of the oncological treatment strategy: (i) the conventional, rectum-first strategy, (ii) the simultaneous strategy (with resection of the primary rectal tumour and the liver metastases (LM) during the same surgical session) and (iii) the liver-first group (Fig. 1).

2.3. Endpoints

2.3.1. Primary endpoint

The study's primary objective was to evaluate the incidence of complete surgical resection rate (R0-R1) at both sites as a function of the oncological strategy. The complete resection rate at both sites was also studied in the subpopulation of patients having completed the full therapeutic strategy (i.e. chemoradiotherapy, surgery and adjuvant chemotherapy).

2.3.2. Secondary endpoints

Post-operative morbidity and mortality were analysed according to the Clavien classification. Non-serious complications were defined as grade I and II Clavien scores and severe complications were defined as grade III and IV scores. Post-operative death was defined as Clavien V [18]. Risk factors for incomplete resection, interval treatment and time without chemotherapy were also studied.

Survival data included the mortality rate, three-year overall survival, mean overall survival, mean disease-free survival and pelvic and hepatic recurrence rates. Survival data were defined with respect to the treatment start date. Mean overall survival was also calculated for the subpopulation of patients having completed the full therapeutic strategy, as defined above.

2.4. Oncological strategies

The oncological strategy was chosen as a function of the characteristics of the SLM and the primary tumour, using the following rules much as possible:

- for class II SLM or non-initially-resectable SLM with locally advanced rectal carcinoma (T3T4 and/or N+), induction chemotherapy was administered first (using Folfox and/or Folfiri and/or targeted therapy, depending on the response to primary chemotherapy). A liver-first strategy was then implemented. Patients received chemoradiotherapy (Folfox or Xelox or Xeloda) after liver surgery. Lastly, rectal surgery was performed.
- for class II SLM or non-initially-resectable SLM and early rectal cancer (T1T2N0), induction chemotherapy was followed by a liver-first approach.
- for class I SLM with locally advanced rectal cancer (T3-T4 and/or N+), Folfox chemoradiotherapy was given first. Simultaneous or rectum-first resection was then performed.
- for class I SLM and early rectal cancer, Folfox chemotherapy was followed by simultaneous or rectum-first resection.

Chemoradiotherapy consisted of radiotherapy (45 Gy in 25 fractions over a 5-week period) and chemotherapy (800 mg/m^2 oral capecitabine twice daily or a simplified Folfox protocol (85 mg/m^2 oxaliplatin + a simplified LV5FU2 regimen every two weeks for the duration of the radiotherapy)) prior to rectal resection. No chemotherapy was performed between the end of the radiotherapy and the day of surgery.

Perioperative chemotherapy was defined as three months of chemotherapy before and after liver resection [3]. For all patients, the tumour response to preoperative chemotherapy was assessed

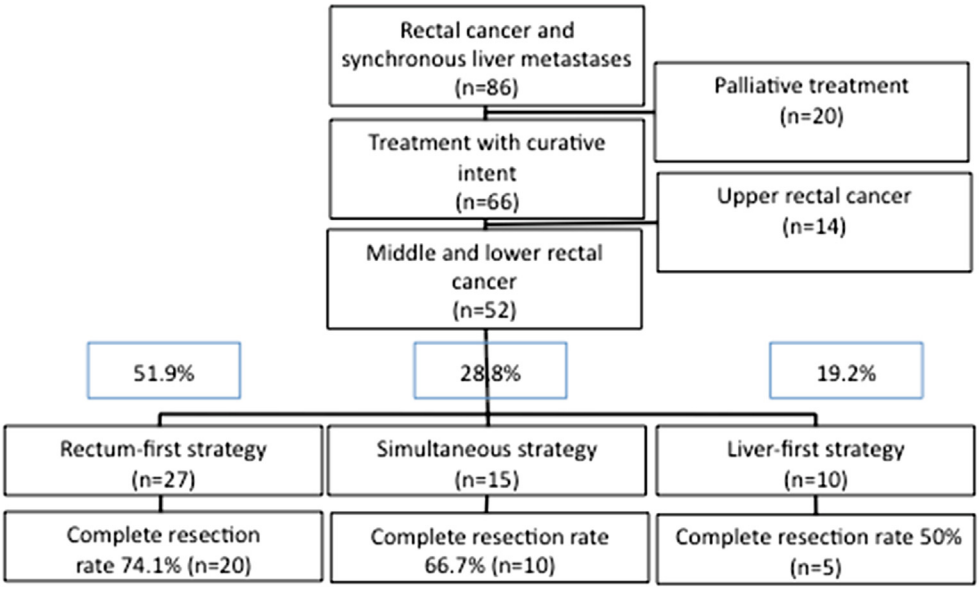

Fig. 1. Study synopsis, patient disposition and treatment group.

with CT and classified by applying the Response Evaluation Criteria in Solid Tumors criteria [19].

2.5. Surgery

2.5.1. Liver surgery

Patients underwent class I or class II hepatectomy as a function of the segments involved, in-flow, out-flow and the liver remnant volume. Intra-operative ultrasound was used to define the final characteristics of the liver nodules and was always performed by the same operator (JMR). The same surgeon performed all liver resections (JMR). The resections were variously anatomical or non-anatomical (depending on the tumour type and the requirement for clear margins).

Patients having undergone two-stage hepatectomy were included in the rectum-first group.

Ultrasound-guided radiofrequency tumour ablation was used to ensure complete resection (especially for left lobe lesion clearance in bilobar SLM) [20].

2.5.2. Rectal surgery

Laparoscopic and laparotomy strategies were used. The type of surgery depended on the tumour site, sphincter involvement and the potential for negative distal and circumferential margins. For all procedures, total mesorectal excision was performed [21,22].

2.6. Histological findings

For the rectum, the pathological stage (ypTNM) was recorded according to the TNM system. The circumferential margin was considered to be positive if the microscopic tumour extension was one mm or less away. The distal margin was considered to be positive if the macroscopic tumour extension was one cm or less away [23].

Complete liver resection (R0) was defined as the presence of clear margins in the liver specimen.

2.7. Statistical analysis

A chi-squared test or Fisher's exact test was used to compare categorical variables, whereas Student's t test or the Mann–Whitney test was used to compare quantitative variables. A univariate analysis was performed (using the afore-mentioned tests) to determine risk factors for incomplete resection. Overall survival was defined as the time between the treatment start date and the date of death or last follow-up visit. Disease-free survival was defined as the time between the treatment start date and any recurrence (whether local or remote) or the last follow-up visit. Survival distributions were estimated using the adjusted Kaplan–Meier method, with inverse probability of treatment weighting. To determine the impact of the strategy on i/Ro resection rate for sites (rectum and liver), ii/overall morbidity rate and iii/overall survival, propensity score calculation was performed. Three scores were conceived from pre-strategy variables: one between “rectum first” and “simultaneous” strategies; one between “rectum first” and “liver first” strategies; one between “simultaneous” and “liver first” strategies. For each endpoint, two analyses were made: the first without propensity score (PS) and the second matched on the PS. All variables that differed significantly ($p < 0.20$) when comparing the 2 groups were included in the logistic model. A p value below 0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS for Windows® software (version 15.0, SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Population

From January 2005 to December 2013, 86 patients were recorded as having rectal cancer with SLM. Sixty-six patients were treated with curative intent and 78.7% of the latter (n = 52) had MLRC (Fig. 1). The group distribution for the MLRC patients was as follows: 51.9% (n = 27) in the rectum-first group, 28.8% (n = 15) in the simultaneous resection group and 19.2% (n = 10) in the liver-first group.

3.2. Epidemiological data and the patients' general status

The patients' characteristics are summarized in Table 1.

3.3. Tumour markers and SLM characteristics

The median serum carcinoembryonic antigen (CEA) level was 17 ± 387.9 ng/ml (range: 2–1265) and the median serum carbohydrate antigen (CA) 19-9 level was 40.5 ± 153.3 U/ml (range: 0–511). There were no intergroup differences in terms of the median serum levels of CEA ($p = 0.5$) or CA 19-9 ($p = 0.8$) (Table 1).

In the present study, 28.8% ($n = 15$ out of 52) of the patients had bilobar SLM and 32.6% ($n = 17$ out of 52) had more than three metastases. The median number of metastases was 3.37 ± 2.5 (range: 1–15). There were no significant intergroup differences in terms of the proportion of patients with bilobar lesions (25.9%, 13.2% and 50% in the rectum-first, simultaneous and liver-first groups, respectively; $p = 0.1$) or the proportion of patients with more than three metastases (25.9%, 20% and 50%, respectively; $p = 0.9$).

3.4. The rate of complete (R0-R1) resection at both sites (the primary endpoint)

The overall complete resection rate (considering both sites) was 67.3% ($n = 35$), with 74% in the rectum-first group ($n = 20$), 66% in the simultaneous resection group ($n = 10$) and 50% in the liver-first group ($n = 5$) ($p = 0.3$ for the intergroup comparison).

When considering the two resected organs separately, none of the three oncological strategies was associated with a markedly worse complete resection rate for the rectum (100%, 100% and 70% for the rectum-first, simultaneous and liver-first groups, respectively; $p = 0.1$) or for the liver (74%, 66% and 80%, respectively; $p = 0.3$). The reasons for deciding not to perform rectal resection in the liver-first group were tumour progression ($n = 2$, one at the liver and one at the rectum) and postoperative complications leading to an alteration in general status ($n = 1$). In the subgroup of patients having completed the full treatment strategy, there were no differences in the complete resection rate (76% ($n = 13$ out of 17), 71% ($n = 5$ out of 7) and 67% ($n = 2$ out of 3) for the rectum-first, simultaneous and liver-first strategies, respectively).

3.5. Risk factors for incomplete resection

Emergency surgery was the only identified risk factor for incomplete resection, since complete resection was not achieved in any of the four patients having undergone emergency surgery (due to obstruction in two cases and perforation in the other two cases, all in the rectum-first group) (Table 2). Two of these patients underwent emergency rectal resection and the other two underwent stent placement followed by chemoradiotherapy and rectal resection.

3.6. Post-operative morbidity and mortality

The overall incidence of postoperative complications after liver

Table 1
Preoperative, epidemiological and oncological characteristics of the study population.

	Rectum-first strategy n = 27	Simultaneous strategy n = 15	Liver-first strategy n = 10	Overall n = 52	p
Epidemiological data					
- Mean age (years)	66.6	61.2	59.7	63.5	0.8
- Men % (n)	59 (16)	53 (8)	80 (8)	61.5	0.2
SLM characteristics					
- Bilobar	26 (7)	13 (2)	50 (5)	27 (14)	0.1
- More than 3 lesions	26 (7)	20 (3)	50 (5)	29 (15)	0.9
tumour marker levels					
- CEA	24.5	3.7	28.9	17	0.5
- CA 19-9	105.5	6.5	48	40.5	0.8
T stage					
- T0	1	0	0	1	0.7
- T1	1	1	0	2	
- T2	3	3	1	7	
- T3	15	9	3	27	
- T4	7	2	3	12	
Neoadjuvant treatment					
-Chemotherapy	7 (2)	20 (3)	70 (7)	23 (12)	0.0003
-Chemoradiation with 5FU	67 (18)	53 (8)	0 (0)	50 (26)	
-Chemoradiaiton with Folfox	26 (7)	27 (4)	30 (3)	27 (14)	
Neoadjuvant treatment					
-Chemoradiotherapy	92.5 (25)	80 (12)	30 (3)	40 (77)	0.0005
-No chemoradiotherapy	2 (7.5)	3 (20)	70 (7)	12 (33)	
Interval treatment					
-Chemoradiotherapy	0	NA	20 (2)	4 (2)	0.09
-Chemotherapy	33 (9)	NA	30 (3)	44 (12)	
-No interval treatment	77 (18)	NA	50 (5)	62 (23)	
N stage					
- N0	30 (8)	47 (7)	43 (3)	37 (18)	0.5
- N1	70 (19)	53 (8)	57 (4)	63 (31)	
Primary resection					
-abdominoperineal excision	41 (11)	13 (2)	0	26.5 (13)	0.2
- Hartmann procedure	11 (3)	13 (2)	29 (2)	14.5 (7)	
- anterior resection	44 (12)	74 (11)	71 (5)	57 (28)	
- TEM	4 (1)	0	0	2 (1)	
Liver resection					
- minor hepatectomy	26 (8)	47 (7)	40 (4)	41 (19)	0.5
- major hepatectomy	32 (10)	20 (3)	40 (4)	36 (17)	
- two-stage resection	12 (4)	0	0	9 (4)	
- unresected liver	30 (9)	33 (5)	20 (2)	34 (16)	

SLM: synchronous liver metastases; CEA: carcinoembryonic antigen; CA-19: carbohydrate antigen 19-9; TEM: transanal endoscopic microsurgery. NA: not applicable.

Table 2
Univariate analysis of risk factors for incomplete resection, as a function of the oncological strategy.

	R0 resection n = 34	R2 resection n = 18	p
Patient-related factors			
• Males, %(n)	52.9 (17)	77.8 (14)	0.1
• Age	61.8	64.4	0.4
• Clinical risk score (1/2/3/4/5), n	11/12/8/3/0	4/4/6/3/1	0.4
Tumour-related factors			
• Emergency surgery, % (n)	0 (0)	22.2 (4)	**0.01**
• Bilateral lesions, % (n)	17.6 (6)	44.4 (8)	0.06
• Number of liver metastases	3.1	3.83	0.4
• ACE	93.5	234.7	0.3
• CA 19-9	88.8	136	0.2
• Response to neoadjuvant treatment	41.7 (14)	33.3 (6)	0.7
Surgery-related factors			
• Postoperative abscess	17.6 (6)	22.2 (4)	0.8
• Anastomosis leak	14.7 (5)	5.6 (1)	0.3

Missing data, World Health Organisation, American Society of Anaesthesiology, chronic obstructive pulmonary disease.
Significantly different value is in bold.

resection was 14% (n = 6 out of 42). The liver complications were related to collections (n = 3), portal thrombosis (n = 1) and biliary fistula (n = 2). The incidence of postoperative complications after liver resection was 10% (n = 2) in the rectum-first group, 15% (n = 2) in the simultaneous resection group and 20% (n = 2) in the liver-first group (p = 0.8).

The incidence of postoperative complications after rectal resection was 38.6% (n = 17). The rectal complications were related to anastomosis or rectal stump leakage (n = 6), pelvis abscess (n = 8) or other medical conditions (n = 4). The incidence of postoperative complications after rectal resection was 29.6% (n = 8) in the rectum-first group, 58.3% (n = 7) in the simultaneous resection group and 60% (n = 3) in the liver-first group (p = 0.1). One patient in the liver-first group (10%) died after rectal resection and one patient in the rectum-first group (5.5%) died after liver resection (Table 3). The overall complication rate after rectal resection was higher than the overall complication rate liver resection (38.6% and 14.2%, respectively; p = 0.01).

3.7. Interval treatment and time without chemotherapy

Eighteen patients (34.6%) received interval treatment. Fourteen received chemotherapy (combined with antiangiogenics in two patients) and four received chemoradiotherapy. The mean interval between the two surgical procedures was 6.4 months (range: 2–12). There were no differences in the complete resection rate when comparing patients who received interval treatment and those who did not (72.2% vs 64.7%, respectively; p = 0.8).

There were no differences between the two-stage groups (i.e. the rectum-first group and the liver-first group) in terms of the time without chemotherapy during the interval (5.2 weeks vs 4.9 weeks, respectively; p = 0.4) and no differences between the three groups in terms of the time without chemotherapy as an adjuvant treatment (5.8, 6.1 and 6 weeks in the rectum-first group, the simultaneous resection group and the liver-first group, respectively, p = 0.1).

3.8. Long-term outcomes

The mean ± SD (95% CI) overall survival time was 60.27 months ± 13.2 (34.8–86.7) in the rectum-first group, 47.6 months ± 13.4 (21.2–74) in the simultaneous resection group and 38 months ± 9.4 (20–57.1) in the liver-first group (p = 0.4). For the subpopulation of patients having completed the full treatment strategy, the mean overall survival was 62 months ± 12.1 (34.8–86.7) in the rectum-first group, 49 months ± 13.1 (22–73) in the simultaneous resection group and 41 months ± 8.1 (22.8–53.2) (p = 0.5) in the liver-first group.

The mean disease-free survival time was 31 months ± 11.2 (9–53.1) in the rectum-first group, 32.8 months ± 13 (7.2–58.3) in the simultaneous resection group and 7.8 months ± 4 (0.1–15.8) in the liver-first group. There were no significant intergroup differences in the disease-free survival rate (p = 0.1).

The mean follow-up time was 42 months ± 4, and the lost-to-follow-up rate was 3.8% (n = 2).

3.9. Analysis with a propensity score

Only one propensity score (PS) (including age (66.6 years vs 61.2 years, p = 0.07) and sex (59% of men vs 53% of men, p = 0.1)) could have been made: those between “rectum first” and “simultaneous” strategies because for the others comparisons no PS was possible. The data are reported in Table 4. The PS has no impact on R0 resection rate (OR (CI95%): 0.71 (0.14–3.56), p = 0.68) and overall survival OR (CI 95%: 1.82 (0.49–6.84), p = 0.38) but it impacts the overall morbidity rate OR (CI95%): 6.3 (1.33–29.95). With the PS, we observed that the simultaneous strategy majors the rate of overall morbidity significantly compared to the rectum-first strategy.

3.10. Limitations of the study

The study had several notable limitations. Firstly, the sample

Table 3
Post-operative complications and complete resection rates.

	Rectum-first strategy n = 27	Simultaneous strategy n = 15	Liver-first strategy n = 10	Overall n = 52	p
Rectal surgery complications					
- No	74.1 (20/27)	41.7 (5/12)	40 (2/5)	61.3 (27/44)	0.06
- Clavien I/II[a]	14.8 (4/27)	33.3 (4/12)	0 (0/5)	18.0 (8/44)	
- Clavien III/IV[b]	11.1 (3/27)	25 (3/12)	40 (2/5)	18.0 (8/44)	
- Clavien V[c]	0 (0/27)	0 (0/9)	20 (1/5)	2.7 (1/44)	
Liver surgery complications					
- No	89.4 (17/19)	84.6 (11/13)	80 (8/10)	85.8 (36/42)	0.9
- Clavien I/II[a]	5.3 (1/19)	7.6 (1/13)	10 (1/10)	7.1 (3/42)	
- Clavien III/IV[b]	0 (0/19)	7.6 (1/13)	10 (1/10)	4.7 (2/42)	
- Clavien V[c]	5.3 (1/19)	0 (0/10)	0 (0/6)	2.4 (1/42)	
Complete resection rate	74.1 (20/27)	66.7 (10/15)	50 (5/10)	67.3 (35/52)	0.6

[a] Clavien I and II: non-serious complications.
[b] Clavien III and IV: serious complications.
[c] Clavien V: death.

Table 4
Analysis with a propensity score.

Event	Rectum first strategy versus simultaneous strategy				Rectum first versus liver first		Simultaneous versus liver first	
	Without propensity score (PS)		With propensity score (PS)		Without propensity score (PS)		Without propensity score (PS)	
	OR (CI95%)	P value	OR (CI95%)	P value	OR (CI95%)	P value	OR (CI95%)	P value
R0 resection for both sites	1 (0.24–4.14)	1	0.71 (0.14–3.56)	0.68	0.63 (0.3–1.33)	0.23	0.4 (0.07–2.18)	0.29
Overall morbidity	3.24 (0.85–12.36)	0.09	6.3 (1.33–29.95)	0.02	1.34 (0.65–2.79)	0.43	0.56 (0.11–2.90)	0.49
Overall survival	1.72 (0.52–5.69)	0.38	1.82 (0.49–6.84)	0.38	1.48 (0.78–2.81)	0.23	1.62 (0.39–6.60)	0.50

size was quite small (n = 52), although it must be borne in mind that no other specific series on MLRC with SLM are available, the nill hypothesis cannot be completely rejected. Secondly, the retrospective design of the series introduced selection bias because the patients were not randomly assigned.

4. Discussion

Once a patient has been diagnosed with MLRC and SLM, the main challenge is choosing the oncological strategy that has the greatest likelihood of achieving complete resection of both the metastases and the main tumour. This involves choosing a strategy for neoadjuvant treatment, surgery and adjuvant treatment. In the specific context of metastatic rectal tumours, this choice commits the patient to several months of treatment. It is therefore logical to seek to identify the right treatment strategy for each individual patient. In the present study, there were no differences between the three oncological strategies in terms of the complete resection rate (74.1%, 66.7% and 50% for the rectum-first, simultaneous and liver-first groups, respectively; p = 0.3). This lack of difference did not appear to be related to differences in the tumour characteristics, since there were no significant intergroup differences in terms of the mean number of lesions per patient or the proportion of patients with bilateral lesions or with more than three lesions. However, the small sample size and thus a lack of statistical power could also account for the absence of a significant difference. Despite this limitation, these outcomes must be taken into account because the present study is the first to compare three oncological strategies for the treatment of tumours requiring radiotherapy. Moreover, it must be noted that even though the difference was not statistically significant, the proportion of patients with bilobar lesions was highest in the liver-first strategy group (50%); this might reflect more aggressive disease and thus a pretreatment selection bias that may have prompted a change in strategy as a function of disease progression and the metastases' distribution. Another interesting observation is that only 70% of the primary tumour in the liver-first group were resected. These outcomes confirm the report by Brouquet al., in which only 50% of rectal primary tumours in the liver-first group were resected [9]. In both series, metastatic progression was one of the most main reasons for not resecting the primary tumour.

The only risk factor for incomplete resection identified here was emergency surgery. Gender, age, the presence of a bilobar lesion, postoperative complications, the number of metastases, tumour marker levels and the clinical risk score were not found to be risk factors (Table 5). The primary tumour was resected in all the patients having undergone emergency surgery, although resection of the liver metastases was not always achieved. This confirms the results of a previous study from our group, in which having more than three metastases and a complicated initial presentation of the primary tumour was found to be a risk factor for incomplete resection. However, the latter study included both colon and rectal tumours [24]. Reddy et al. reported a greater incidence of positive margins for simultaneous resection than for staged resection (14% and 3%, respectively; p = 0.01) [5], and so our present conclusions need to be confirmed in larger series.

In the present study, the three groups did not differ in terms of the complication rate. Nevertheless, simultaneous major hepatectomy and rectal surgery has been identified as a risk factor for morbidity and mortality [5,25], even though the rates appear to be acceptable in some studies [4,26,27]. Martin et al. did not find any differences between simultaneous resection and staged resection in terms of the overall complication rate (56% and 55%, respectively; p = 0.24) [27]. De Haas et al. observed similar mortality rates in simultaneous and staged resection (0% and 0.6%, respectively; p = 0.5) and a lower overall morbidity rate for simultaneous resection than for staged resection (11% and 25.4%, respectively; p = 0.01) [28].

In the present study, there were no intergroup differences in terms of overall (p = 0.4) and disease-free survival (p = 0.1), which thus confirmed other recent reports [6,9,10]. In a series including all types of colon and rectal tumours, Brouquet et al. reported three-year overall survival rates of 58% in the colon–or rectum-first group, 65% in the simultaneous resection group and 79% in the liver-first group [9]. In a LiverMetSurvey-based study, Andres et al. reported a five-year overall survival rate of 48% in the colon–or rectum first group and 46% in the liver-first group (p = 0.9), and a five-year disease-free survival of 30% in the colon-rectum first group and 26% in the liver-first group (p = 0.9) [10]. Moreover, in a series of 22 patients having undergone a liver-first strategy (including 19 with rectal tumours), de Jong et al. did not find any predictive factors for treatment failure (neither the site of the primary tumour, nor the

Table 5
Comparison of data from specific studies of SLM in rectal cancer.

	Brouquet et al. [9]	Van der pool et al. [6]	Andres et al. [10]	The present study
Study population	Upper, middle and lower rectal cancer	Upper, middle and lower rectal cancer	Upper, middle and lower rectum	Middle and lower rectal cancer
Number of patients	81	57	202	52
Rectum-first strategy n(%)/complete resection	35 (48.6)/NR	29 (50.8)/NR	169 (83.6)/NR	27 (51.9)/20 (74.1)
Simultaneous resection n(%)/complete resection	18 (25)/9 (50)	8 (14)/NR	0	15 (28.8)/10 (66.7)
Liver-first strategy n(%)/complete resection	19 (26.3)/9 (47.3)	20 (35)/NR	33 (16.4)/NR	10 (19.2)/5 (50)
Prognostic factors	Postoperative complications, Tumour size >3 cm	Preoperative CEA >200 ng/ml	No intergroup differences in survival	Emergency surgery

NR: not reported.

number and site of the liver metastases) [29].

These data emphasize that the choice of an oncological strategy for SLM remains problematic. Given the observed absence of intergroup differences in the complete resection rate, post-operative morbidity and long-term outcomes in the present study, it is suggested that the treatment strategy should be chosen on a case-by-case basis and as a function of (i) the main oncological problem and (ii) the presence or absence of predictive factors for rectal resection morbidity (even though there are no data in support of this position) [30]. In patients with widespread liver disease and a well-localized rectal tumour, a liver-first strategy should be adopted. In patients with locally advanced rectal cancer and limited liver disease, a conventional rectum-first strategy should be adopted. Lastly, for locally advanced rectal cancer and extensive liver disease, the treatment strategy will depend on the response to initial chemotherapy.

The treatment of MLRC with SLM is still a major clinical challenge. Even though our present findings should be interpreted with caution (given the small sample size), the present study is the first to address this question in MLRC.

In conclusion, there were no differences in short and long-term outcomes when considering three oncological strategies. No one oncological strategy should be favoured for all cases MLRC with SLM and similar outcomes suggests proper treatment selection for all three groups. Emergency surgery was the only risk factor for treatment failure ($p = 0.01$), and so no other specific data were of value in choosing the oncological strategy. The strategy should be chosen, based on the oncological emergency (rectum-first or liver-first), the need for a quick and optimal oncological management, predictive factors for morbidity in rectal surgery and MDT discussion.

Ethical approval

Ethical Approval was given by the local ethical committee (294574).

Author contribution

Study design: all authors.
Data collections: Charles Sabbagh, Tiana Ravololoniaina.
Data analysis: All authors.
Writing: Charles Sabbagh, Jean-Marc Regimbeau.
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