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ORIGINAL ARTICLE – COLORECTAL CANCER

Rectal Outcomes After a Liver-First Treatment of Patients with Stage IV Rectal Cancer

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ABSTRACT

Background. The treatment of patients with metastatic rectal cancer remains controversial. We developed a reverse strategy, the liver-first approach, to optimize the chance of a curative resection. The aim of this study was to assess rectal outcomes after reverse treatment of patients with metastatic rectal cancer.

Methods. From May 2000 to November 2013, a total of 34 consecutive selected patients with histology-proven adenocarcinoma of the rectum and liver metastases were prospectively entered into a dedicated computerized database. All patients were treated via our reverse strategy. Rectal and overall survival outcomes were analyzed.

Results. Most patients presented with advanced disease (median Fong clinical risk score of 3; range 2–5). One patient failed to complete the whole treatment (3 %). Rectal surgery was performed after a median of 3.9 months (range 0.4–17.8 months). A total of 73.3 % patients received preoperative radiotherapy. Perioperative mortality and morbidity rates were 0 and 27.3 % after rectal surgery. Severe complications were reported in two patients (6.1 %): one anastomotic leak and one systemic inflammatory response syndrome. The median hospital stay was 11 days (range 5–23 days). Complete local pathological response was observed in three patients (9.1 %). The median number of lymph nodes collected was 14. The R0 rate was 93.9 %. There was no positive circumferential margin. After a mean follow-up of 36 months after rectal surgery, 5-year overall survival was 52.5 %. Five patients experienced pelvic recurrence.

Conclusions. In our cohort of selected patients with stage IV rectal cancer, the reverse strategy was not only safe and effective, but also oncologically promising, with a low morbidity rate and high long-term survival.

Between 15 and 25 % of patients with colorectal cancer present synchronous liver metastasis (CRLM), a condition associated with worse survival rates.[1–3] In these patients, by convention classified as stage IV (distant metastasis), management is multidisciplinary, involving surgery of the primary and of the liver metastasis, pelvic radiotherapy, and chemotherapy.[4] However, the sequence of these treatments is still a matter of debate, especially for patients with rectal cancer.[5,6]

Since 1999, a reverse strategy for managing patients with stage IV colorectal cancer has been developed at our institution.[7–10] The rationale behind this strategy is to control the CRLM at the same time as the primary cancer,

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optimizing the chances of a curative liver resection.[7] Treatment starts with a very active three to four drug chemotherapy (usually oxaliplatin, CPT-11, 5-fluorouracil [5-FU], and leucovorin), avoiding any delay as often observed after complicated colorectal surgery.[11] Liver surgery is done next and colorectal surgery is performed last, after radiotherapy if indicated.

Although this approach is intuitively sound and has been adopted by many centers around the world, the specific pelvic outcomes of patients after reverse treatment are poorly documented.[12–16] This point is of interest because these patients are primarily treated by liver-targeting chemotherapy and undergo rectal surgery later in the course of their treatment.

The aim of this study was to assess the outcomes of patients with rectal cancer and liver metastasis after reverse treatment, with a focus on rectal data.

MATERIALS AND METHODS

Patient Selection and Treatment Strategy

Selected patients with stage IV histology-proven adenocarcinoma of the rectum ($\leq$15 cm from the anal verge) were prospectively entered into a dedicated database from May 2000 to November 2013. All potentially resectable stage IV rectal cancer patients were discussed during a multidisciplinary tumor board. The decision of the reverse strategy was made during this meeting, including surgeons, oncologists, radio-oncologists, radiologists, and pathologists.

The selection criteria were: patients with advanced liver disease, patients without advanced rectal cancer (requiring, e.g., extended pelvic dissection), and patients fit to undergo chemotherapy and surgery.

All the included patients underwent a reverse treatment strategy, also known as the liver-first approach, as previously reported.[7–10] Patients received 2–8 cycles (median 3 cycles) of chemotherapy before liver resection. Drug combinations included OCFL (oxaliplatin, CPT-11, 5-FU, and leucovorin, $n = 22$), OCFL-like with capecitabine replacing 5-FU–leucovorin ($n = 2$), FOLFIRI–bevacizumab (leucovorin–5-FU–irinotecan, $n = 3$), FOLFOX–bevacizumab (leucovorin, 5-FU, and oxaliplatin, $n = 3$), FOLFOX–cetuximab ($n = 2$), and CFL (without oxaliplatin, $n = 1$).

At the end of the second cycle of chemotherapy, new radiological studies were performed confirming the absence of progression of the liver lesions, and the hepatic resections were performed 2–3 weeks later. Additional courses of neoadjuvant chemotherapy were provided only if the metastases were considered not resectable or if further chemotherapy was likely to confer a surgical advantage.[7] After the liver surgery, ideally 3–4 weeks later, pelvic radiochemotherapy (associating capecitabine) was initiated, when indicated (T3 and T4 or N+), with a total dose of 28 $\times$ 1.5 Gy for 5.5 weeks, and rectal surgery was performed 6–8 weeks later. Upper rectal cancers (10–15 cm from the anal margin) were also considered for preoperative radiochemotherapy when indicated.

Five patients who underwent simultaneous rectal and liver resections in the study period were excluded from this analysis.

Studied Data

The distance of the tumor from the anal margin was assessed by rigid rectoscopy or digital examination. In addition, all patients had a total colonoscopy. The preoperative T and N status was evaluated by a multimodal strategy: endoscopic ultrasonography and/or magnetic resonance imaging (MRI). The M status was assessed by triple-phase computed tomographic scan, associated to MRI and/or biopsy in case of unclear diagnosis. Advanced metastatic disease was defined as a clinical risk score (CRS) of 3 or more, according to the classification of Fong et al.[17]

The operative time was defined as the time between the skin incision and the skin closure. A low anterior resection was defined as a rectal resection below the peritoneal reflection, including a total mesorectal excision. An anterior resection was defined as a rectal resection above the peritoneal reflection (tumor located in the high rectum), including a partial mesorectal excision. The necessity of diverting stoma was decided by the surgeon on a case-by-case basis. A conversion was defined as the need to finish a laparoscopic procedure by an open approach.

The morbidity was evaluated by the Clavien–Dindo classification.[18]

Regarding the circumferential resection margins, a minimum of 0.1 cm was required to achieve a R0 resection.

Follow-up was performed at 6, 12, and 18 months and then annually, using tumor markers, endoscopy, and radiology.

Statistical Analysis

Data were expressed as median (range).

Overall survival rate and cumulative incidence of local recurrence were calculated by the Kaplan–Meier method by SPSS software, version 18 for Windows (IBM, Armonk, NY). Overall survival and local disease-free survival were computed from the date of rectal resection.

TABLE 1 Patient demographics

Characteristic	Reverse treatment ($n = 33$)
Gender, *n* (%)	
Male	19 (57.6 %)
Female	14 (42.4 %)
Age, years, median (range)	57 (38–78)
Body mass index (kg/m^2), median (range)	22.5 (17–29.4)
ASA score, median (range)	2 (1–3)
Distance of rectal tumor from anal margin, cm, median (range)	10.5 (0–15)
Preoperative TNM staging	
T4	8 %
N+	72 %
M+ (liver)	100 %
Characteristics of liver metastasis	
No. of lesions, median (range)	5 (1–20)
Bilobar metastasis	63.6 %
Maximum size, cm, median (range)	3 (1–15)
Characteristics of liver surgery, *n* (%)	
Portal embolization	15 (45.5 %)
Staged hepatectomy	6 (18.2 %)
Major hepatectomy (≥3 segments)	25 (75.8 %)
Level of CEA before treatment, ng/mL, median (range)	21.4 (1.7–1190)
Clinical risk score, median (range)	3 (2–5)
1	0 (0 %)
2	7 (21.2 %)
3	19 (57.6 %)
4	4 (12.1 %)
5	3 (9.1 %)
Preoperative rectal radiochemotherapy	73.3 %

ASA American Society of Anesthesiologists, *CEA* carcinoembryonic antigen

TABLE 2 Perioperative outcomes

Characteristic	Reverse treatment ($n = 33$)
Operative time, min, median (range)	260 (120–420)
Type of resection	
LAR	71 %
AR	12.9 %
APR	16.1 %
Protective stoma	15 (45.5 %)
Estimated blood loss, mL, median (range)	500 (250–700)
Transfusion rate	2 (6 %)
Surgical approach	
Laparotomy	61.3 %
Laparoscopy	38.7 %
Conversion	3 %
Mortality	0
Morbidity	27.3 %
Hospital stay, days, median (range)	11 (5–23)

LAR low anterior resection, *AR* anterior resection, *APR* abdominoperineal resection

RESULTS

Patient Characteristics

During the study period, 34 patients with stage IV rectal cancer underwent the reverse-strategy approach. One patient with rectal cancer did not complete the whole treatment (3 %); this patient presented with a CRS of 4, underwent a liver-first approach, developed early liver recurrence after hepatic resection, and died before the rectal surgery. Because this patient did not undergo the whole treatment, these data were excluded from further analysis.

The patients' demographics are summarized in Table 1. The population had a normal body mass index and a low American Society of Anesthesiologists score. The median distance of rectal tumor from the anal margin was 10.5 cm.

Patients had a median of five liver metastases, with 63.6 % being bilobar disease. The median CRS was 3 (range 2–5), and 78.8 % of patients had a score of 3 or more, reflecting the severity of the metastatic disease. Most patients had previously undergone a major hepatectomy (75.8 %).

The median time between liver and rectal surgeries was 3.9 months (range 0.4–17.8 months).

Regarding the preoperative rectal staging, only 8 % of patients had a T4 tumor, but 72 % of patients had an N+ status. Preoperative radiochemotherapy was given to 73.3 % of patients (uT3/uT4 and/or uN+).

Perioperative Outcomes

The median operative time was just over 4 h (Table 2). Seventy-one percent of patients underwent a low anterior resection with total mesorectal excision, with a protective stoma rate of 45.5 %. Median blood loss was 500 mL, with two patients requiring an intraoperative transfusion (transfusion rate of 6 %).

More than a third of patients received a minimally invasive approach. One procedure was converted from laparoscopy to open surgery during the pelvic dissection, which was difficult because of a rectal stent.

There was no perioperative mortality. Nine patients developed a complication after rectal surgery (27.3 %). Four of these were grade I according to Clavien–Dindo classification (postoperative ileus, wound dehiscence, ascites, diffuse edema). We recorded three grade II

TABLE 3 Pathological outcomes

Outcome	Reverse treatment
Pathological data	
pT0	9.7 %
pT1	0
pT2	16.1 %
pT3	58.1 %
pT4	16.1 %
pN+	64.5 %
Lymph node, median (range)	14 (0–33)
Distal margin, cm, median (range)	2.75 (0.1–7.5)
Positive margins	2 (6.1 %)
Circumferential margin, cm, median (range)	0.6 (0.1–3)
Positive margins	0

SD standard deviation

complications: pneumonia, fever of unknown origin, and a deep venous thrombosis. Regarding severe complications (grade III or higher), there was one anastomotic leak that required a reoperation (grade IIIb) and case of systemic inflammatory response syndrome that required a short stay in the intensive care unit (grade IVa).

The median hospital stay was 11 days (range 5–23 days).

Pathologic Assessment

Three patients had a complete rectal pathological response (9.1 %; Table 3). In two cases a complete pathological response was observed after pelvic radiochemotherapy, and in one case after preoperative chemotherapy (OCFL) without radiotherapy. There were 16.1 % of pT4 tumor as well, and 64.5 % of patients had a pN+ status. Of note, 81.3 % of patients presented with chemotherapy-induced hepatic injury (with a wide range of lesions, from discrete steatosis to severe portal fibrosis).

The median number of collected lymph nodes was 14 (range 0–33). We observed an R1 rate of 6.1 %, with two patients presenting a positive distal margin. The first patient required an emergency intervention for an occlusive and perforated rectal tumor 11 days after the initial hepatectomy. The second patient became occlusive 40 days after the liver resection. Of note, neither of the two patients had undergone preoperative local radiochemotherapy. They both presented with local recurrence.

There was no positive circumferential margin.

Oncological Outcomes

Twenty-one patients were alive after a mean follow-up of 36 ± 41.2 months from the rectal surgery (i.e., 45 ± 39.6 months after the beginning of the reverse treatment). The 1-, 3-, and 5-year overall survival rates were 81.6, 68, and 52.5 %, respectively (Fig. 1), from the rectal surgery. In addition, the 1-, 3-, and 5-year overall survival rates were 96.8, 68.3, and 61.4 %, respectively, from the liver surgery (Fig. 2).

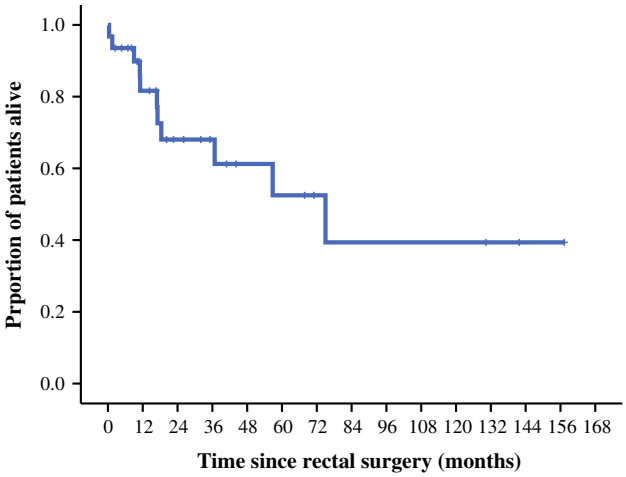

FIG. 1 Overall survival rate since rectal surgery

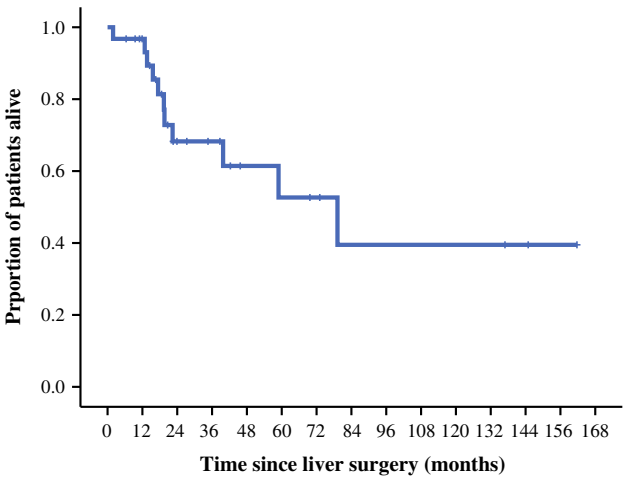

FIG. 2 Overall survival rate since liver surgery

Concerning local outcomes, five pelvic recurrences were observed after a mean time of 12.2 ± 6.5 months. One of the recurrences was initially managed by a transanal resection only. This patient had experienced a complete clinical and pathological response after the pelvic radiochemotherapy, had a further recurrence 11 months after the second surgery, and underwent an abdominoperineal resection with a final pT3Nx. In addition, two other patients presented with recurrence. One of them had pT3N1 disease after a laparoscopic abdominoperineal resection. The other patient had pT3N2 disease after a low anterior resection. Both had received preoperative radiochemotherapy. Of note, the circumferential margins were 0.1 cm in both cases.

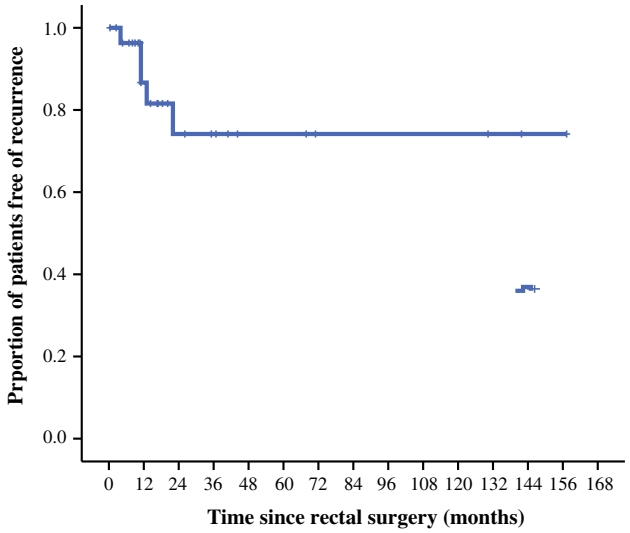

FIG. 3 Proportion of patients free of local recurrence since rectal resection

The local disease-free survival rate is reported in Fig. 3.

DISCUSSION

The treatment of patients with synchronous CRLM is still a matter of debate. Experts recognize that a combined surgical and oncological approach is the only way to obtain long-term survival.[7,11] However, the timing of the different steps of the treatment remains controversial, and three options can be identified: standard (rectal-first approach), reverse (liver-first approach, which is in fact a liver-oriented chemotherapy-first approach), and simultaneous (i.e., combined rectal and liver resection during the same operation) strategies.[4–6,11,12,19–21]

Since 1999 we have developed the so-called reverse strategy, and here we report our experience for stage IV rectal cancer, with a focus on the pelvic outcomes.[7–10] In the present series of selected patients, the overall safety and efficacy of the reverse approach were demonstrated, with a low morbidity rate and good long-term survival, even in patients with advanced metastatic disease. The theoretical advantages of the reverse approach appeared to be fulfilled, including the use of the most effective chemotherapies for both the rectum and liver, the treatment of the prognosis-limiting site (the liver) first, the absence of chemotherapy delay because of rectal morbidity, and the option of performing state-of-the-art rectal radiochemotherapy before the rectal resection.[4] Among these, we consider as important the advantage of avoiding the delay in starting chemotherapy, which can be seen in case of septic pelvic complications (i.e., anastomotic leakage), which occurs in between 12 and 27.4 % of patients after rectal resection.[22–24] Such a delay could have terrible prognostic consequences in a group of patients threatened by the progression of the liver metastases beyond all possibility of cure.

Supporters of combined liver and rectal resections argue that the simultaneous approach also prevents a delay of chemotherapy and avoids the need for a second surgical procedure (rectal resection).[25] In addition, in case of symptomatic rectal tumor (obstruction, bleeding, perforation), an emergency rectal resection may be necessary anyway and may appear as a contraindication for reverse treatment.[20] Of note, for obstructive lesion, a rectal stent is also an option to consider, although it can lead to a more difficult local resection because of the induced inflammatory response.[21]

To illustrate the simultaneous approach, Vigano et al. reported 32 patients who underwent a combined hepatic and rectal resection.[4] They found overall mortality and morbidity rates of 2.8 and 36 %, respectively. In addition, they reported a 5-year overall survival rate of 59.3 %; these data are in agreement with our own results and have been confirmed by others.[15] Comparing a staged approach (rectal-first approach) and synchronous liver resection, another group showed no significant difference in terms of survival.[19] These data were confirmed in a review.[6] However, it was suggested that staged resections might result in better outcomes.[26] Indeed, the risk of major complications seems, in contrast, higher in simultaneous compared to staged resections, even if controversial data continue to animate the debate.[6,11,21,25,27]

Beyond overall survival, the primary aim of this study was to report local outcomes. Others have shown good overall data after a liver-first approach for patients with rectal cancer and CRLM.[12,13] However, local results, as surrogate of the quality of the resection, are poorly reported.[15] In a recent study, the risk factors for morbidity of staged rectal resection were similar to those for standard proctectomy.[16] With a morbidity rate of 27.3 % (and only two severe complications) and no mortality, our results compare favorably to other studies focusing on stage IV rectal cancer and also compared to nonmetastatic colorectal resection.[13,15,16,28,29] The reverse strategy does not seem to have a negative impact on the complication rate after the rectal surgery. A potential problem addressed by colorectal surgeons is portal hypertension resulting from liver resection or chemotherapy-induced hepatic injury.[6] Although the majority of patients in this series had chemotherapy-induced lesions, only one patient presented a complication directly related to a liver-first chemotherapy (postoperative ascites, requiring us to leave in intra-abdominal drainage for several days).

The local R0 rate in our patients was within the range previously reported, despite an average delay of almost 4 months between the liver and the rectal surgery.[13] The drawbacks of a long delay between secondary and primary

tumor resection and the risk of local progression thus remain hypothetical.[14] In addition, some patients might experience a complete local response, as we report here (9.1 %). Finally, it is likely that with the classic rectal-first approach, some borderline resectable liver metastases would have become unresectable.[16]

Although our study hints at encouraging outcomes, it has several limitations. First, the number of patients is small, and the time spans over several years. During this period, chemotherapy has evolved and might have contributed to the good outcomes.[2] The population studied here had some favorable features, such as low body mass index, low American Society of Anesthesiologists score, and low T4 rate; it is thus difficult to generalize the results to all patients with stage IV rectal cancer. However, our patients had also a high CRS and high rate of bilobar disease.

As a criticism of the reverse approach, it may be argued that it is unreasonable to leave the primary tumor in situ because of the risk of local complications leading to the interruption of the treatment plan. Indeed, obstruction or perforation may develop during the reverse treatment, especially in case of local advanced rectal tumor. Even if this risk is low, we observed two cases in our series(both patients in the end, with positive margins and local recurrence).[13] This emphasizes the necessity of good patient selection before starting a multimodal reverse strategy and of careful timing of all steps. The reverse strategy might be better adapted to advanced liver metastatic disease than to locally advanced rectal cancer.

As for the comparison between the reverse and the traditional strategy, a recent systematic review on the topic of synchronous CRLM could not show the superiority of any one of the approaches, adding to the consensus that the treatment plans should be defined in a multidisciplinary meeting on an individual basis.[6,20,21] The intention-to-treat analysis was not included, however, and we believe that it is in the intention-to-treat perspective that the benefit of the reverse approach should be investigated: in the present series, at least half of the patients had disease that would not have been considered resectable with an up-front surgical operation and would have been treated with palliative intent. The present study demonstrates that the reverse approach does not jeopardize pelvic outcomes, thus opening the door to prospective randomized trials in which the intention-to-treat effect can be investigated.

CONCLUSIONS

We presented a relatively large cohort of patients with stage IV rectal cancer. The reverse strategy was not only safe and effective but also appeared oncologically at least equivalent to traditional strategies. Indeed, both low morbidity and good long-term outcomes were observed. In order to confirm the present findings, and to investigate a possible impact of intention to treat, randomized studies appear justified.

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