Simultaneous or Staged Resection for Synchronous Liver Metastasis and Primary Rectal Cancer: A Propensity Score Matching Analysis

Elias Karam
Hôpital Trousseau: Hopital Trousseau
Petru Bucur
Hôpital Trousseau: Hopital Trousseau
Camille Gil
Hôpital Trousseau: Hopital Trousseau
Remy Sindayigaya
Hôpital Trousseau: Hopital Trousseau
Nicolas Tabchouri
Hôpital Trousseau: Hopital Trousseau
louise Barbier
Hôpital Trousseau: Hopital Trousseau
Urs Pabst-Giger
University of Tours: Universite de Tours
Pascal Bourlier
Hôpital Trousseau: Hopital Trousseau
Thierry Lecomte
Hôpital Trousseau: Hopital Trousseau
MOUSSATA Moussata
Hôpital Trousseau: Hopital Trousseau
Sophie Chapet
Hôpital Bretonneau: Hopital Bretonneau
Gilles Calais
Hôpital Bretonneau: Hopital Bretonneau
Mehdi ouaissi (m.ouaissi@chu-tours.fr)
Hôpital Trousseau: Hopital Trousseau https://orcid.org/0000-0002-0906-4428
Ephrem Salame
Hôpital Trousseau: Hopital Trousseau

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Abstract

Background:

Colorectal cancer is the third most common cancer in France and by the time of the diagnosis, 15 to 25% of patients will suffer from synchronous liver metastases. Surgery associated to neoadjuvant treatment can cure these patients, but few studies focus only on rectal cancer. This study was meant to compare the outcomes of patients who underwent a simultaneous resection to those who underwent a staged resection (rectum first or liver first) in the University Hospital of Tours, France.

Methods:

We assessed retrospectively a prospective maintained data base about the clinical, pathological and survival outcomes of patients who underwent a simultaneous or a staged resection in our center between 2010 and 2018. A propensity score matching was used, considering the initial characteristics of our groups.

Results:

There were 70 patients (55/15 males, female respectively) with median age 60 (54-68) years. After matching 48 (69%) of them underwent a staged approach and 22 (31%) a simultaneous approach were compared. No differences were found in terms of morbidity (p = 0.210), overall survival (p = 0.517) and disease-free survival (p = 0.691) at 3 years after matching. There were significantly less recurrences in the simultaneous group (50% vs 81.8%, p = 0.026)

Conclusions:

Simultaneous resection of the rectal primary cancer and synchronous liver metastases is safe and feasible with no difference in terms of survival.

Background

Colorectal cancer (CRC) is the 3rd most common cancer in France and represents about 20% of cancers [1, 2]. Upon diagnosis, 15 to 25% of patients have synchronous liver metastases (SLM). Although only 20% of CRC + SLM patients are eligible for surgical resection, a 5-year overall survival of 60% can be achieved when surgery is feasible [3]. Whether CRC and SLM resection should be performed separately or simultaneously remains controversial [4, 5]. In patients with initially resectable SLM, three strategies can be proposed. The “conventional” or “historical” staged strategy consists in initially treating CRC then SLM resection with perioperative chemotherapy. It allows to control the evolution of CRC and decreases the risk of bowel obstruction or rectal symptoms [6, 7, 8]. The “liver-first” strategy consists in initially resecting liver metastases with perioperative chemotherapy (CT), followed by CRC management. It is particularly used for patients with significant metastatic liver disease and an asymptomatic primary tumor [9]. Specifically for rectal cancer, recently some authors proposed an “interval strategy”, consisting in long-course radio-chemotherapy (RT/CT), followed shortly after completion by resection of liver metastases and 6 to 8 weeks after the end of RT, rectal surgery [10]. Another possibility is the simultaneous CRC + SLM resection with promising results in well-selected patients with few co-morbidities and little extensive liver damage (mainly minor hepatectomies) [11, 12, 13, 14, 15, 16, 17]. Numerous retrospective studies have compared the simultaneous or staged strategies. Their findings have been reported in 5 recent reviews and meta-analyses [12, 18, 19, 20, 21]. CT and RT protocols have evolved over time and laparoscopic procedures now yield similar oncologic outcomes to open procedures [22, 23, 24]. However, these studies do not differentiate between rectal and colonic primary and surgical techniques are different, with specific operating time, morbidity and mortality. Some studies targeting rectal cancer [24], including mostly rectal tumors [25], or having

performed specific subgroup analyses on rectal cancer [16] have shown contradictory results in the different strategies previously described. Only one prospective randomized clinical trial compared these two strategies but only 38% of included patients had rectal cancer. More recent studies show a better survival for rectal cancers with SLMs compared to colon cancer with SLMs [26], safety and satisfactory oncological outcomes of simultaneous resection in both colonic and rectal cancers with SLMs [27]. Valdimarsson et al. [28] suggest simultaneous resection for colorectal cancer and SLMs show no difference in terms of survival compared to bowel first strategy, even though they experienced more complications. The aim of this study was to compare simultaneous and staged managements of rectal cancers with SLMs in terms of post-operative morbidity and mortality, recurrence, and survival and between 2010 and 2018 in the University Hospital of Tours, France.

METHODS

Methods

Study population

Of 500 patients treated for rectal cancer at the University Hospital of Tours between January 2010 and December 2018**,** 70 patients with rectal cancer and SLM were selected. Exclusion criteria were an unachievable R0 resection (on rectum and SLMs), extra-hepatic localization, intraoperatively discovered hepatic localization, liver metastases appearing more than 6 months after rectal cancer diagnosis. SLMs were defined as all liver lesions discovered before or simultaneously with primary rectal cancer. Patients had a thoraco-abdominal CT scan and a liver magnetic resonance imaging (MRI) scan as part of the extension assessment. Rectal cancer assessment included clinical examination (digital pelvic exam, anoscopy) and paraclinical investigations (complete colonoscopy with biopsies, rectal endoscopic ultrasound (EUS), pelvic MRI). Evaluation of T stage was dependent on EUS, according to Hildebrandt et al. [29] and preoperative liver and pelvic MRI. These investigations confirmed rectal cancer location (low, 0 to 5 cm from the anal verge; mid, 5 to10; upper, 10 to 15) and assessed lymph node involvement.

Preoperative treatment-oncologic bridge treatment (figure 1A et 1B and Figure 1 supplementary data)

5 fluorouracil or capecitabin-based Chemotherapy (CT) (5FU) were administered concomitantly with RT to 16 patients according to our guidelines for patients with mid/low rectal tumors and/or T3/4 rectal tumors. Short-course RT was chosen for 14 patients to have closely sequenced sessions because of the extent of the hepatic disease, age, or personal reasons. 22 patients underwent CT alone because of no indication for RT and six patients underwent RT alone because of CT contra-indications. Twelve patients underwent surgery without neoadjuvant treatment: ten because of small-sized rectal tumours and liver SLM, two because of cardiology-related contra-indications. Overall, 58 out of 70 patients had a neoadjuvant treatment, 39 in the staged surgery group and 19 in the simultaneous group. Twelve patients did not receive any NA treatment because of small size tumours or contraindications. Concerning the neoadjuvant treatment in each group, 5 fluorouracil or capecitabin-based chemotherapy were administered concomitantly with RT (50 Gy in 25 fractions over five weeks) according to institutional recommendations for patients with mid/low rectal tumors and/or T3/4 rectal tumors. Short-term RT was chosen because of the extent of liver disease, age, or social reasons to have closely sequenced therapy sessions. CT alone was performed when there was no need for rectal RT and RT alone was performed because of CT contraindications.

Concerning the staged surgery group, bridge treatment was CT alone for 5 patients mostly depending on SLM size, associated in six cases with a pre-operative portal embolization. Twenty patients had CT alone after second surgery, and 13 patients had CT only after both surgeries were performed, including two patients who underwent hepatic stereotaxic RT. Decision to deliver post-operative CT was based on tumor histologic type and/or surgical margins.

Concerning the simultaneous surgery group, 18 patients underwent adjuvant CT, with no stereotaxic RT associated, based on tumor histologic type and/or surgical margins.

Evaluation of tumor response

All patients had a clinical re-evaluation six weeks after the end of neo-adjuvant therapy with standard clinical examination (digital exam, anal examination). EUS was performed by the same team as the initial evaluation. Evolution of pre-treatment T and N staging was re-evaluated by pelvic MRI scan according to the 1.1 version RECIST criteria [30]. SLMs were reevaluated after neoadjuvant treatment by CT scan and MRI scan.

Choice of surgical procedure

Patients underwent a simultaneous approach, either through laparotomy or laparoscopy, if the surgical procedure on the liver was not a major hepatectomy (<3 segment of liver). On the contrary, if liver metastases implied a major hepatectomy (>3 segment or required a preoperative embolization), a two-staged approach was preferred.

Moreover for the low and advanced rectal cancer requiring abdominal perineal resection or coloanal anastomosis, surgical stage approached was preferred.

Surgical procedures

Patients underwent mechanical bowel preparation before surgery. For rectal surgery, laparoscopic approach was the standard approach. For T4 tumors, open approach was preferred [31]. A medial-to-lateral approach was used. Specimens were retrieved from abdominal cavity via a small abdominal incision [31]. Mechanical colorectal or manual colo-anal anastomoses (side-to-end or end-to-end) were performed depending on tumor level. Total or partial intersphincteric resection for very low rectal cancer was performed whenever feasible. Otherwise, a perineal abdominal amputation was performed. Upper rectal cancer underwent partial mesorectal excision with a 5 cm margin from the lower limit of the tumor. Other patients underwent standard TME. A protective loop ileostomy was performed routinely for mid and low rectum tumours.

Surgery was performed for curative intent. Whenever necessary, liver resection was combined with radiofrequency ablation (RFA). Major hepatectomy was defined as a liver resection comprising 3 or more contiguous liver segments. Portal vein embolization was considered if calculated remaining liver volume was insufficient (< 30% total liver volume) [32]. Two-stage hepatectomy involved initial resection of all left liver metastases with ligation of the right portal vein or embolization of the right portal vein in the postoperative period. Four to 6 weeks after first surgery, a right or extended hepatectomy was performed. Liver transection was carried out using squeeze-clamp technique and ultrasound dissection to expose residual vessels or glissory sheaths, which were ligated with 4-0 vicryl or sealed using LigaSure technology [33, 34, 35, 36]. Intraoperative ultrasonography was routinely performed to guide SLM resection.

Pathology results

Primary tumors were analyzed using a standardized protocol [37]. TNM classification was used according to the 8th edition of American Joint Committee of Cancer (AJCC). Circumferential and distal resection margins were defined as positive (R+) if less than 1 mm and negative (R0) if more than 1 mm to the tumor.. Total or partial mesorectal excision, colloid component degree, differentiation grade, vascular, lymphatic or perinervous emboli, liver fibrosis, liver steatosis and capillary obstruction syndrome were stated in pathology report.

Short-term outcomes

Anastomotic leakage was defined and graded according to the International Study Group of Rectal Cancer [38]. Any clinical (sepsis, peritonitis, emission of gas, pus, or feces from the pelvic drain, purulent discharge per anus, or rectovaginal fistula) and/or biological suspicion of AL led to an early CT-scan. Management included antibiotics, radiologic or transanal drainage, and/or early abdominal redo surgery [39]. Patients presenting with postoperative bile leakage were treated with antibiotics and radiological or surgical drainage [40]. Short-term 30-day postoperative complications were ranked according to Clavien Classification [41].

Long-term outcomes

Recurrence-free and overall survivals were analyzed. Postoperative follow-up included clinical, biochemical, and radiological assessments every three months during first postoperative year, then every six months up to five years postoperatively and every year up to ten years. Surviving patients were assessed for disease recurrence and site of recurrence. Follow-up data were obtained from medical records and direct patients' consultation.

Statistical analysis

Propensity score matching (PSM) using nearest-neighbor method was performed to match patient who underwent simultaneous resection of liver metastasis to those who underwent staged procedures. PSM model was generated using preoperative risk factors reported to impair patient's survival, namely, surgical difficulty (i.e., minor, or major hepatectomy) and underlying liver fibrosis. Qualitative variables are presented in percentages and compared using $\chi 2$ test with Bonferroni correction whenever necessary. Quantitative variables are presented in medians and interquartile range and compared using Student or Wilcoxon test. Kaplan-Meier method was used to estimate recurrence-free survival and overall survival, which were compared using the Log-rank test. Continuous variables were compared using ANOVA or nonparametric ANOVA tests. This study was conducted according to the ethical standards of the Committee on Human Experimentation of our institution and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [42].

Results

Demographic and pre-operative characteristics (Table 1)

Seventy patients with rectal cancer and SLM were included, 48 (69%) underwent a staged procedure and 22 (31%) a simultaneous procedure. There were more male patients (sex-ratio: 15/55) with median age of 60 (54-68). Upon diagnosis, rectal tumours were mainly T3 (72.9%) with bilobar liver metastasis in 48.6% of patients and a median number of 2 metastases. There was no difference between each group regarding medical history, except BMI which was significantly higher in the staged surgery group (median 25.6 with $p = 0.0244$). Overall, 74.3% of patients underwent CT, 22.9% long-course RT and 20% short-course RT, with no differences between both groups (NS). After PSM, patients who underwent simultaneous liver resection were significantly older than those who underwent staged procedures (65 (60-77) years old *vs.* 59 (52-65) years old; $p = 0.012$). After PSM, patients who underwent simultaneous liver resection there were significantly more male than staged group (80% vs 57.1%; $p = 0.021$).

Intra-operative parameters (Tables 2 and Table S1 supplementary data)

For all series, 51.4%, 12.9% and 35.7% of patients underwent all laparotomy, all laparoscopic, and mixed procedures, respectively. Conversion to laparotomy occurred overall in 23.5% because of excessive bleeding or difficulties performing dissection. Complete TME was performed in 67.1% of patients and abdominoperineal resection (APR) in 22.9% (NS). Anastomoses were mainly mechanical using staples (94.4%). Pringle manoeuvre lasted a median time of 30.5 (19-45) minutes and there were 34% of diverting loop ileostomas, with no differences between both groups. In

contrast, all laparoscopy procedures were significantly higher in the simultaneous surgery group (31.8% vs 4.2%, p = 0.0032). There were more major hepatectomies in the staged surgery group (50% vs 4.5%, p = 0.0001) and more minor hepatectomies in the simultaneous surgery group (95.5% vs 50%, p = 0.0001). In the staged surgery group, rectum first (RF) and liver first (LF) procedures were performed in 37 (77%) and 11 (23%) patients. After PSM, patients in the "staged" group were more likely to undergo mixed procedures (18.2% vs. 0%; p = 0.040).

Rectum first (RF) and liver first (LF) procedures were analysed separately in the staged surgery group (**Table S1**). There were no differences concerning the surgical approach even though there were zero laparoscopy procedures in the LF group. Conversion rate, complete TME rate, APR rate were similar, anastomosis was mechanical in 73% and 72.7% concerning respectively RF and LF groups (NS). There were significantly more major hepatectomies in the RF group (64.9% vs 0%, p = 0.0002) and more minor hepatectomies in the LF group compared to the RF group (100% vs 35.1%, p = 0.0002). No differences were found for the duration of the Pringle manoeuvre nor the diverting stoma rate, and there was a six-month median period between rectal and liver procedures.

Post-operative outcomes (Table 3)

The overall complications rate was 45.7% with significantly more complications in the staged surgery group (70.8% vs 40.1%, p = 0.0329). For the staged procedures, complications in the first and second hospital stay were added. Complications stages I-II occurred in 34.3% and stages III-IV in 27.1% of the patients. There were significantly more sepsis complications in the staged surgery group (all linked to anastomotic fistulas) 31.3% vs 9.1% (p = 0.0398), more CT scan drainage in the staged surgery group (16.7% vs 0%, p = 0.0498) because of anastomotic fistulas. There were significantly more CT scan drainages in the staged surgery group (16.7% vs 0%, p = 0.0498) of peri-anastomotic collections, but also higher percentages of surgical drainages for fistulas, fistulas treated with only antibiotics and bilomas (with CT-guided or surgical drainages), even though those were not significantThere were also more fistula surgical drainages, bilomas, CT and surgical bilomas drainages in the staged surgery group- However, these differences were not statistically significant different. There was no post-operative hepatic failure. The hospital stay was significantly higher in the staged surgery group with a median of 25 days vs 12 days (p = 0.0249). After PSM, there was no difference regarding postoperative complications rate or hospital length of stay between both groups.

Pathology results (Table 4)

Rectal tumours were mainly T3 (70%) and N1 (45.7%) with medians of 25 (17-33) harvested lymph nodes and 1 lymph node metastasis. There was a median of two liver metastases resected, rectal and liver margins were positive in 11.4% and 24.3% respectively. In the staged surgery group, there was more liver fibrosis, more liver steatosis and more capillary obstruction syndrome compared to simultaneous group with no significative difference. There were no significant differences regarding the number of harvested lymph nodes or the number of metastatic lymph nodes or the number of positive rectal margins. Concerning molecular biology KRAS, BRAF mutation were observed in 20% and 1.4% of patients without statistical difference between two groups staged and simultaneous groups (13.6 vs 22.7%, 2.1% vs 0% , p=0.569; p=1.000). For microsatellite instability only one patient was MSI

(1.8 %), and was in staged group.

Concerning liver pathology, after PSM patients in the "staged" group had more often positive liver resection margins (18.2% *vs.* 0%; p =0.040).

Rectum first (RF) and liver first (LF) results were analysed separately in the staged surgery group (**Table S2**). Tumours were T3 in 67.6% of the RF and 63.6% of the LF procedures and N1 in 43.2% of the RF and 45.4% of the LF procedures. There were more R1 liver resections in contact with the liver tissue in the RF group (77.8% vs 75%), less R1 rectal

resections on the lateral margin in the RF group (50% vs 100%), more liver fibrosis and steatosis in the RF group (35.1% vs respectively 9.1% and 18.2%), less capillary obstruction syndrome in the RF group (16.2% vs 27.3%), none of these results were significant. The median size of the liver metastasis was higher in the RF group but not significantly (35 vs 21 millimetres).

Late postoperative and survival outcomes (Table 5, figure 2,AB)

Median follow-up was 28 months (19-42) overall. After propensity score matching, recurrences were significantly higher in the staged surgery group (81.8% *vs.* 50%; p = 0.026) and tended to occur mainly in the liver (63.6% vs. 36.6%, p = 0.070). Recurrence occurred mainly in 1 site (51.4%) with a 15-month median period until recurrence. Recurrences were mostly treated with chemotherapy (55.7%). After PSM, overall survival at 3 and 5 years as well as disease free survival at 3 years were comparable between the “staged” and “simultaneous” groups (**figure 2A,B**).

Discussion

Our present case series of patients treated with staged or simultaneous resection of rectal cancer and synchronous liver metastasis (SLM) showed no difference in terms of morbidity and survival after PSM. A significantly higher recurrence rate occurred in patients who underwent staged therapy.

Modern therapeutic approach for rectal cancer with resectable SLM combines rectal surgery (TME) with neoadjuvant RT or RCT and liver surgery with perioperative CT in complex therapeutic sequences. Any complication might alter the timing of interventions. Primary colonic cancers do not always need neoadjuvant treatment before resection, which is impossible in case of SLMs. Primary rectal cancer surgery is associated with higher morbidity in retrospective series on colorectal carcinomas and SLMs [36, 43]. One can postulate that associating RT and total mesorectal excision to liver surgery might dangerously increase complication rate and affect long term survival.

In the current study, 70 patients were managed at a tertiary centre of expertise for colorectal and liver surgery and clinical outcomes were investigated. Our groups were not initially comparable, considering major differences between groups characteristics. One of these major differences was in the choice of surgical approach : because we opted for a staged approach when the liver resection was predicted to be extensive, we had significantly less major hepatectomies in the simultaneous surgery groupTo solve this problem, we used propensity score matching. After doing so, we observed older patients in the staged surgery group and no other significant differences. Before matching, morbidity rate was higher in the staged surgery group, most probably explained by the higher rate of major liver resections (three or more segments) as observed in the literature [44] and length of stay was shorter. However, after PSM, morbidity rates and length of stay were comparable in both groups.

Ghiasloo et al. [45] observed a higher morbidity rate after a staged surgical approach, especially when primary rectal cancer was operated on first ("rectum first"). However, not only rectal cancer patients but also colon cancer patients were included in this large retrospective study. No data were presented regarding a detailed outcome of the subgroup of rectal cancer patients and thus their interpretation regarding rectal cancer patients is limited. In the most recently published study by Abelson et al. from 2017 [15], the subgroup analysis of patients with rectal cancer and SLM (New York State Department of Health Statewide Planning and Research Cooperative System database) showed no significant perioperative outcome differences between simultaneous or staged therapy regarding major perioperative complications such as anastomotic insufficiency. In addition, patients who underwent simultaneous resection were significantly less likely to have a prolonged hospital stay (OR = 0.25; 95% CI = 0.14-0.45) and high hospital costs (OR = 0.26; 95% CI = 0.14-0.45).

In 2015, Silberhumer et al. [14] reported no differences in morbidity and mortality - regardless of whether rectal cancer was operated on first or simultaneous rectal and SLM surgery was performed. No difference was found either, regardless of whether only a limited or extended liver resection had to be performed.

In the only randomised trial comparing the staged and simultaneous approaches to colorectal cancer and SLMs [46], there was no difference between the two approaches in terms of morbidity. In particular there was no difference between patients who had at least one severe complication (Clavien-Dindo stages III to IV). The rate of patients who had at least one serious complication was 18% for rectal resection and 21.7% in the case of simultaneous rectal and SLM resection. However, they did not differentiate between the extent of liver resections in their study and their group of staged operations included only rectal first procedures.

We found more positive resection margin on the liver and a higher recurrence rate in the staged surgery group after PSM. Survival was not affected; however, consequences may happen in a larger cohort. Maybe staged resection was used when more complex liver resections were needed, leading to a worse surgical clearance of the tumour.

Regarding overall survival and tumour recurrence, we did not find any difference after PSM. Several large cohort studies reported the same overall and disease-free survival regardless of whether the resection was simultaneous or two-stage, and whether liver or bowel were operated on first [14, 34, 45]. In contrast, two studies reported better overall survival for the two-stage approach. These two retrospective studies did not find simultaneous surgery to be an independent factor for worse prognosis in their multivariate analysis, even though patients in these two studies received significantly more CT in the two-stage therapy group [14, 34]. In contrast, Slupski et al. [47], found patients in the simultaneous resection group having a better overall survival. This result could be explained by a significantly higher disease burden in patients undergoing a two-stage approach. For De Haas et al. [35], simultaneous resection of colorectal carcinoma and SLMs had a lower morbidity rate than a two-stage resection, but the simultaneous approach was also found in a multivariate analysis as an independent predictor of tumor recurrence three years later.

Our results seem to fit with the existing literature, confirming feasibility and safety of simultaneous resection of rectal cancer with SLM. Furthermore, survival did not differ between both groups even though positive resection margin and recurrence rate were higher in the staged surgery group. Our findings need to be confirmed by other large cases series. To the very best of our knowledge, this present case series is one of the first to focus only on rectal cancer with SLMs.

Limitations of this study include its retrospective study design, initially non comparable groups which we compensated using PSM and a changing therapeutic approach using conventional open or laparoscopic surgery.

Conclusion

However, these weaknesses reflect the natural evolution of standard of care over time and are also a reflection of the clinical practice. Simultaneous resection of rectal primary cancer and synchronous liver metastases is safe and feasible with no difference in terms of survival.

Abbreviations

Colorectal Cancer CRC

Synchronous liver metastasis SLM

Magnetic resonance imaging MRI

Cumputed tomography CT

Radio chemo therapy RCT

Radiotherapy RT

Chemotherapy CT

Neoadjuvant NA

Total Mesorectal Excision TME

American Society of Anesthesiology score ASA

Endorectal Ultrasound EUS

Radio frequency ablation RFA

Abdominoperineal resection APR

Rectum first RF

Liver first LF

Propensity score matching PSM

Declarations

Ethics approval and consent to participate

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. This study was approved by the local comity of informatics and liberty (CIL) (n° 2020-067).

Consent for publication

Not applicable

AUTHORS CONTRIBUTION:

Study concept and design: Ouaissi

Acquisition of data: Ouaissi, Karam, Gil, Quetel

Analysis and interpretation: Ouaissi, Tabchouri, Karam

Drafting the manuscript: Ouaissi, Tabchouri, Karam, Gil

Critical review of the manuscript: Bourlier, Pabst-Giger, Lecomte, Salame, Bucur, Moussata, Calais, Barbier, Chapet

Statistical analysis: Ouaissi

Administrative, technical, and material support: Ouaissi

Study supervision: Ouaissi

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Competing interests

Conflict of Interest: All Authors except Thierry Lecomte have no conflict of interest.

For Thierry Lecomte: Advisory board: AMGEN, Servier, SANOFI, Merck Serono; Honoraria: AMGEN, Servier, SANOFI; Travel: AMGEN, Servier

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1: Demographic and preoperative characteristics of the 70 patients with rectal cancer and synchronous liver metastases according to their surgical management

	Before matching				After matching		
	Overall population	Staged surgery	Simultaneous surgery	P	Staged surgery	Simultaneous surgery	P
N (%)	70 (100)	48 (69)	22 (31)		22 (50)	22 (50)	
Age (years), median ± IQR	64 (54 – 68)	61 (54 – 67)	65 (60 – 77)	0.0644	59 (52-65)	65 (60-77)	**0.012**
• ≥ 60 years, n (%)	46 (65.7)	28 (58.3)	18 (81.8)	0.0634	11 (50)	18 (81.8)	**0.026**
• < 60 years, n (%)	24 (34.3)	20 (41.7)	4 (18.2)		11 (50)	4 (18.2)	
Sex ratio (Female/Male)	15/55	13/35	2/20	0.1208	8/14	2/20	**0.021**
BMI (kg/m2), median ± IQR	25.4 (23 – 28)	25.6 (23 – 28.8)	24.8 (23.4 – 27.2)	**0.0244**	24.4 (22.9-26.7)	24.8 (23.2-27.5)	0.740
ASA score, n (%)							
- 1	25 (35.7)	14 (29.2)	11 (50)	0.2342	8 (36.4)	9 (40.9)	
- 2	40 (57.2)	30 (62.5)	10 (45.5)		14 (63.6)	10 (45.5)	0.155
- 3	5 (7.1)	4 (8.3)	1 (4.5)		0	3 (13.6)	
Arteriopathy, n (%)	2 (2.9)	2 (4.2)	0	1.0000	1 (4.6)	0	0.312
Diabetes, n (%)	11 (15.7)	9 (18.8)	2 (2.9)	0.4825	3 (13.6)	2 (9.1)	0.635
Tumor diagnosis, n (%)							
Bleeding	38 (54.2)	23 (48)	15 (68.1)	0.1300	10 (45.5)	15 (68.2)	0.128
Weight loss	11 (15.7)	6 (12.5)	5 (22.7)	0,3035	4 (18.2)	5 (22.7)	0.709
Rectal adenocarcinoma location, n(%)							
- Upper (10-15 cm)	21 (30)	14 (29.2)	7 (31.8)	0,6572	3 (13.6)	6 (27.3)	
- Mid (5-10 cm)	28 (40)	18 (37.5)	10 (45.5)		10 (45.5)	10 (45.5)	0.449
- Low (2-5 cm)	21 (30)	16 (33.3)	5 (22.7)		9 (40.9)	6 (27.3)	
T stage, n (%)							
-T1	5 (7.1)	2 (4.2)	3 (13.7)	0.4345	0	3 (13.6)	
-T2	6 (8.6)	5 (10.4)	1 (4.5)		2 (9.1)	1 (4.6)	

							0.283
-T3	51 (72.9)	36 (75)	15 (68.1)		18 (81.8)	15 (68.2)	
-T4	8 (11.4)	5 (10.4)	3 (13.7)		2 (9.1)	3 (13.6)	
Liver metastasis							
Bilobar (n, %)	34 (48.6)	25 (35.7)	9 (41)	0.4442	13 (59.1)	9 (40.9)	0.228
Number patients >3 metastasis	19 (27.1)	15 (31.3)	4 (18.1)	0.3860	7 (31.8)	4 (18.2)	0.296
Number of metastasis (median, IQR)	2 (1 – 4)	3 (1 – 4)	2 (1 – 2)	0.7100	3 (1-4)	2 (1-3)	0.226
Neoadjuvant chemotherapy, n (%)	52 (74.3)	36 (75)	16 (72.7)	1.0000	17 (77.3)	19 (86.4)	0.434
Portal embolization, n (%)	6 (8.6)	3 (6.3)	3 (13.6)	0.3699	1 (4.6)	3 (13.6)	0.294
Neoadjuvant radiation therapy, n (%)							
- Long-course radiotherapy *	16 (22.9)	11 (23)	5 (22.7)	1.0000	5 (22.7)	5 (22.7)	0.999
- Short-course radiotherapy **	14 (20)	9 (18.8)	5 (22.7)		5 (22.7)	5 (22.7)	

IQR : interquartile range * with chemotherapy ** without chemotherapy

Table 2: Intraoperative parameters characteristics of the 70 patients with rectal cancer and synchronous liver metastases according to their surgical management

	Before matching				After matching		
	Overall Population	Staged surgery	Simultaneous surgery	P	Staged surgery	Simultaneous surgery	P
Number of patients	70	48 (69)	22 (31)	-	22	22	-
All procedure by laparoscopy, n (%)	9 (12.9)	2 (4.2)	7 (31.8)	**0.0032**	7 (31.8)	7 (31.8)	0.999
Laparotomy, n (%)	36 (51.4)	27 (56.2)	9 (41)	0.3050	6 (27.3)	6 (27.3)	0.999
Mixed*, n (%)	25 (35.7)	19 (39.6)	6 (27.2)	0.4229	4 (18.2)	0	**0.040**
Conversion to laparotomy, n (%)	8/34 (23.5)	6/21 (28.6)	2/13 (15.4)	0.4438	5 (22.7)	9 (40.9)	0.195
Complete TME, n (%)	47 (67.1)	35 (72.9)	12 (54.5)	0.1721	18 (81.8)	12 (54.6)	0.052
Partial TME, n (%)	23 (32.9)	13 (27.1)	10 (45.5)		4 (18.2)	10 (45.4)	
Abdominoperineal resection, n (%)	16 (22.9)	11 (22.9)	5 (22.7)	1.000	5 (22.7)	5 (22.7)	0.999
Anastomosis technique, n (%)							
Mechanical (stapled)	51/54 (94.4)	35/37 (94.6)	16/17	1.000	21 (95.5)	20 (90.9)	0.549
Manual	3/54 (5.6)	2/37 (5.4)	1/17		1 (4.5)	2 (9.1)	
Liver surgery, n (%)							
Minor hepatectomy	45 (64.3)	24 (50)	21 (95.5)	**0.0001**	21 (95.5)	20 (90.9)	0.549
Major hepatectomy	25 (35.7)	24 (50)	1 (4.5)		1 (4.5)	2 (9.1)	
Associated radiofrequency ablation	7 (10)	7 (14.6)	0	0.0893	2 (9.1)	1 (4.5)	0.549
Duration of Pringle maneuver (minutes), median ± IQR	30.5 (19 – 45)	30 (25-45)	13 (11-18)	0.1409	25 (0-30)	13 (0-63)	0.999
Diverting stoma, n (%)	34 (48.6)	21 (43.8)	13 (59.1)	0.3050	7 (31.8)	12 (27.3)	0.128
Delay between first and second surgery (months), median ± IQR	6 (4 – 8)	6 (4-8)	-	-	2 (0-5)	-	

IQR : interquartile range

Major hepatectomy : resection of 3 segments or more

Hybrid : laparoscopy and laparotomy

Table 3: Postoperative parameters of the 70 patients with rectal cancer and synchronous liver metastases according to their management

	Before matching				After matching		
	Overall Population	Staged surgery	Simultaneous surgery	P	Staged surgery	Simultaneous surgery	P
N (%)	70 (100)	48 (69)	22 (31)	-	22	22	
Complications	43 (61.4)	34 (70.8)	9 (40.1)	**0.0329**	16 (72.7)	12 (54.6)	0.210
Clavien I-II	24 (34.3)	18 (37.5)	6 (27.2)	0.5882	15 (68.2)	10 (45.6)	0.128
Clavien III-IV	19 (27.1)	16 (33.3)	3 (13.6)	0.1462	1 (4.6)	2 (9.1)	0.549
Sepsis, n (%)	17 (24.3)	15 (31.3)	2 (9.1)	**0.0398**	7 (31.8)	6(27.3)	0.741
Anastomotic fistula, n (%)	17 (24.3)	15 (31.3)	2 (9.1)	**0.0398**	2 (9.1)	2 (9.1)	0.999
Antibiotics only, n (%)	5 (7.1)	4 (8.3)	1 (4.5)	1.000	2 (9.1)	2 (9.1)	0.999
CT scan Drainage for colorectal complications	8 (11.4)	8 (16.7)	0	**0.0498**	0	0	**-**
Surgical drainage laparotomy for colorectal complications	4 (5.7)	3 (6.3)	1 (4.5)	1.000	0	0	-
Hepatic failure, n (%)	0	0	0	1.000	0	0	-
Biloma, n (%)	4 (5.7)	4 (8.3)	0	0.3008	2 (9.1)	0	0.148
Biloma CT-guided drainage, n (%)	3 (4.3)	3 (6.3)	0	0.5467	0	0	-
Biloma surgical drainage, n (%)	1 (1.4)	1 (2.1)	0	1.000	1 (4.6)	0	0.312
Pulmonary complications, n (%)	5 (7.1)	3 (6.3)	2 (9.1)	0.6463	0	2	0.148
Neurological complications, n (%)	3 (4.3)	2 (4.2)	1 (4.5)	1.000	0	1 (4.6)	0.311
Ileus, n (%)	9 (12.9)	6 (12.5)	3 (13.6)	1.000	1 (4.6)	3 (13.6)	0.294
Hospital stay (days), median	21 (15 – 29)	25 (18-30)*	12 (9-19)	**0.0249**	8 (6-15)	12 (8-28)	0.298

IQR: interquartile range, CT: computed tomography

Post-operative hepatic failure defined as bilirubine > 50 micromol/L and prothrombine < 50%

*Hospitalization stay days included two hospitalization of the two staged

Table 4: Pathology results of the 70 patients with rectal cancer and synchronous liver metastases according to their management

	Before matching				After matching		
	Overall Population	Staged surgery	Simultaneous surgery	P	Staged surgery	Simultaneous resection	P
N (%)	70 (100)	48 (69)	22 (31)	-	22 (50)	22 (50)	
Rectal pT stage, n (%)							
- pT0	5 (7.1)	3 (6.3)	2 (9.1)		2 (9.1)	2 (9.1)	0.791
- pT1	3 (4.4)	3 (6.3)	0	0.691	0	1 (4.6)	
- pT2	5 (7.1)	4 (8.2)	1 (4.5)		2 (9.1)	1 (4.6)	
- pT3	49 (70)	32 (66.7)	17 (77.3)		17 (77.3)	16 (72.7)	
- pT4	8 (11.4)	6 (12.5)	2(9.1)		1 (4.6)	2 (9.1)	
Rectal pN stage, n (%)							
- pN0	23 (32.9)	15 (31.3)	8 (36.3)		11 (50)	9 (40.9)	0.810
- pN1	32 (45.7)	21 (43.7)	11 (50)		8 (36.4)	10 (45.5)	
- pN2	15 (21.4)	12 (25)	3 (13.7)		3 (13.6)	3 (13.6)	
Number of lymph nodes harvested, median ± IQR	25 (17 – 33)	24 (18-38)	26 (15-32)	0.803	27 (20-47)	26 (14-32)	0.423
Number of lymph nodes metastasis, median ± IQR	1 (0 – 4)	1 (0-4)	1 (0-2)	0.335	2 (0-4)	1 (0-2)	0.696
Rectal resection positive margin, n (%)	8 (11.4)	6 (12.5)	2 (9.1)	1.000	1 (4.6)	2 (9.1)	0.549
Number of liver metastasis, median ± IQR	2 (1 – 4)	2 (1-6)	2 (1-3)	0.207	3 (2-6)	5 (3-6)	0.453
Liver resection positive margin, n (%)	17 (24.3)	13 (27.1)	4 (18.1)	0.553	4 (18.2)	0	**0.040**
Percentage of liver metastasis necrosis, median ± IQR	50 (23 – 68)	50 (25-70)	45 (4-50)	0.297	40 (25-90)	25 (20-90)	0.789
Liver fibrosis, n (%)	16 (22.9)	14 (29.2)	2 (9.1)	0.074	1 (4.6)	2 (9.1)	0.550
Liver steatosis, n (%)	23 (32.9)	16 (33.3)	7 (31.8)	1.000	2 (9.1)	7 (31.8)	0.062
Capillary obstruction syndrome, n (%)	16 (22.9)	9 (18.8)	7 (31.8)	0.227	0	2 (9.1)	0.148
Largest size of liver metastasis (mm), median ± IQR	30 (18 – 40)	35 (18-40)	24 (15-31)	0.179	20 (10-39)	24 (16-41)	0.392
Molecular biology, n (%)							

KRAS mutation	14(20)	8 (18.8)	5 (22.7)	0.529	3 (13.6)	5 (22.7)	0.698
BRAF mutation	1 (1.4)	1 (2.1)	0	1.000	0	0	1.000
Microsatellite instability (MSI)	1/55 (1.8)	1/39 (2.5)	0	1.000	1/18 (5)	0	0.450
Unknown statu of microsatellite instability	15 (21.4)	9 (18.3)	6 (27.3)	0.532	4 (18.2)	6 (27.3)	0.720

IQR : interquartile range

Table 5. Late postoperative outcomes of the 70 patients with rectal cancer and synchronous liver metastases according to their management

	Before matching				After matching		
	Overall Population	Staged surgery	Simultaneous resection	P	Staged surgery	Simultaneous resection	P
N (%)	70 (100)	48 (69)	22 (31)	-	22 (50)	22 (50)	-
Oncological results							
Adjuvant chemotherapy, n (%)	56 (80)	38 (79.1)	18 (32.1)	1.000	7 (31.8)	6 (27.3)	0.741
Recurrence, n (%)	51 (72.9)	40 (83.3)	11 (50)	**0.0078**	18 (81.8)	11 (50)	**0.026**
Rectal	5 (7.1)	5 (10.4)	0	0.1727	2 (9.1)	0	0.148
Liver	32 (45.7)	26 (54.2)	6 (27.2)	**0.0425**	14 (63.6)	8 (36.6)	0.070
Carcinosis	11 (15.7)	8 (16.7)	3 (13.6)	1.000	2 (9.1)	3 (13.6)	0.635
Number of recurrences sites, n (%)							
1	36 (51.4)	26 (54.2)	10 (45.5)	0.5604	16 (88.9)	10 (90.9)	0.862
2	8 (11.4)	7 (14.6)	1 (4.5)		2 (11.1)	1 (9.1)	
3	1 (1.4)	1 (2.1)	0		0	0	
Time to recurrence (month), median ± IQR	15 (11 – 20)	17 (11-21)	13 (11-14)	0.3568	13 (6-25)	8 (5-11)	0.465
Median of follow up (months) ± IQR	28 (18 – 39)	28 (19-42)	20 (13-34)	0.0990	28 (16-38)	16 (8-38)	0.285
Overall survival at 3 years (%)	86%	85%	42%	0.0749	68%	62%	0.517
Overall survival at 5 years (%)	44%	77%	54%		45%	46%	
Disease free survival at 3 years (%)	20%	19%	4.5%	0.6851	7%	10%	0.691
Disease free survival at 5 years (%)	3.5%	24%	0%		-	-	
Recurrence treatment, n (%)							
Surgery	11 (15.7)	9 (18.8)	2 (9.1)	0.2998	6 (27.3)	2 (9.1)	0.118
Chemotherapy	39 (55.7)	31 (64.6)	8 (36.4)	0.7063	13 (59.1)	8 (36.4)	0.131
Radiotherapy	11 (15.7)	7 (14.6)	4 (18.2)	0.2220	3 (13.6)	4 (18.2)	0.680

Delayed fistula, n (%)	2 (2.9)	0	2 (9.1)	**0.0431**	0	0	-

IQR : interquartile range

Figures

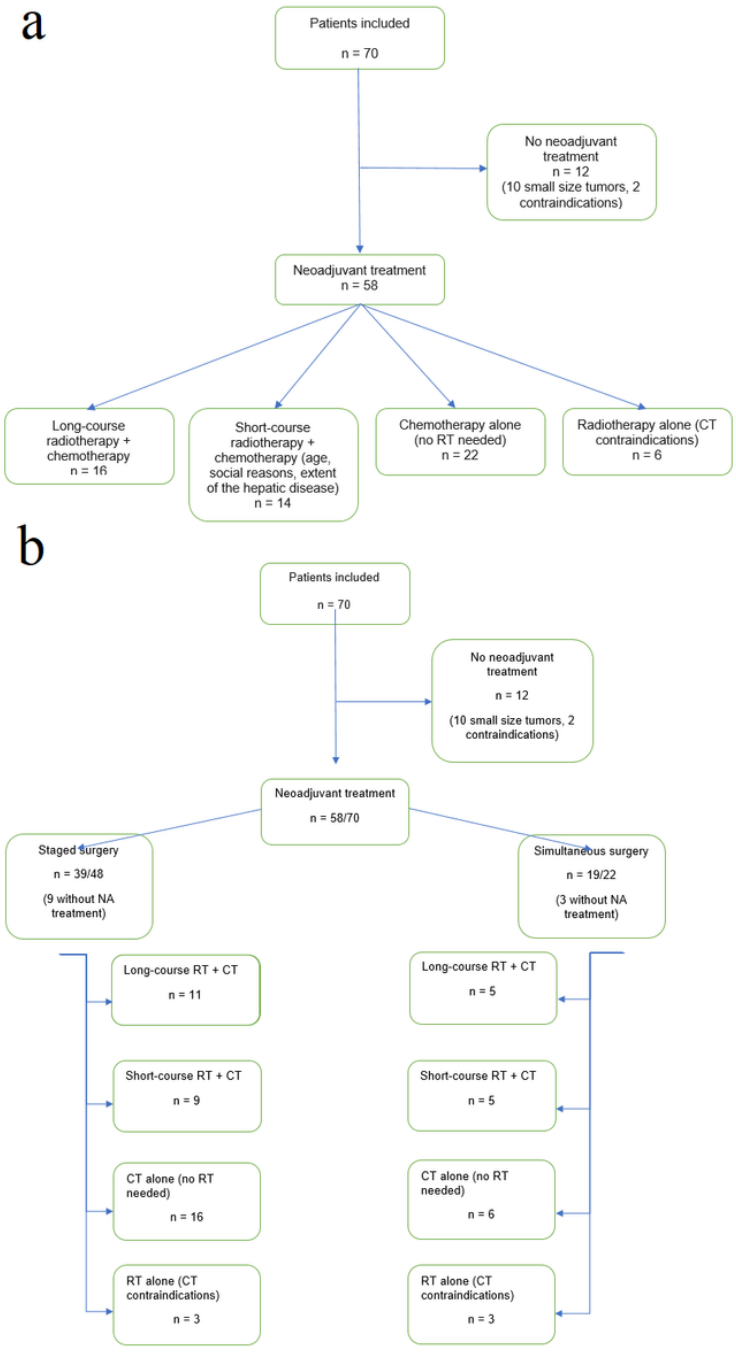

Figure 1

A: Flowchart of 70 patients with rectal cancer and synchronous liver metastases according to their neoadjuvant management

B: Comparison flowchart of patients' neoadjuvant managements between staged and simultaneous group

Figure 2

A: Comparison of overall survival between staged surgery group (solid line) and simultaneous surgery group (dashed line).

Staged surgery group (solid line) and simultaneous surgery group (dashed line). Comparaison of overall survival in staged and simultaneous surgery.

X axis : time (months). Y axis : percentage surv

B: Comparison of disease-free survival between staged surgery group (solid line) and simultaneous surgery group (dashed line).

Staged surgery group (solid line) and simultaneous surgery group (dashed line). Comparison of disease free survivals between staged and simultaneous surgery groups.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FigureS1.docx
- TableS1RFLFV51.docx
- TableS2pourRFetLFV5121.docx