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CICLO XXXIV

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A comparison between Open, Laparoscopic and Robotic Techniques in General Surgery with a particular focus on Colorectal and Hepatobiliary surgery

Settore Scientifico Disciplinare: MED/18

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INTRODUCTION

a. Background

Colorectal cancer (CRC) is one of the most common malignant neoplasms in the world and the third leading cause of cancer-related death in developed countries [1]. In Italy, as the Globocan database shows, it is the third most common cancer for both genders with an incidence of 29,3 per 100 000 person-year [2]. Rectal located-tumours comprehend about 35% of the CRC [3].

In addition to the patients presenting with distant metastasis (about 20-34%) [3], it is estimated that 20-50% of patients who undergo curative colorectal resection and, eventually, neoadjuvant/adjuvant therapies, will develop a metachronous recurrence [4,5]. The liver is the most common site of distant spread of CRC. Liver metastases occur in up to 60% of those patients and they could present in synchronous (13-25%) or metachronous (up to 75%) manner [6,7].

Within multimodality and multidisciplinary treatment, surgery is a cornerstone in the management of CRC, both primary and metastatic, whenever technically feasible and oncologically appropriate [8].

In rectal surgery, the total mesorectal excision (TME) is a gold standard and the crucial part of the anterior resection of the rectum. It includes the complete removal of the tumour along with the draining lymphatics maintaining an intact mesorectal fascia [9]. Moreover, the TME is particularly challenging in several conditions including patients with a narrow pelvis, male, obese patients, patients treated with neoadjuvant radiotherapy. All these factors could potentially negatively affect operative time, specimen quality, and, finally, survival rates [10].

In liver surgery, due to technical and technological improvements and perioperative care, indications to liver resection have been widened over the past 3 decades maintaining acceptable morbidity and mortality rates [11]. Unfortunately, only about 25% of the metastatic patients could be resected with negative margins preserving an adequate liver remnant volume [7]. Despite a high recurrence rate, up to 80%, with 10-15% of early recurrence and disease-specific deaths, for these patients, the expected 5-years survival rate reaches about 40-74% and the cure rate about 20% [11,12]. In the case of synchronous presentation, the indication to treat primary cancer first, the metastasis (liver-first approach) or both of them together needs to be evaluated based on patients symptoms, number and location of liver lesions and a multidisciplinary evaluation should be mandatory [13,14].

Reduction of surgical trauma, incision-related complications, length of hospital stay, and better cosmetic outcomes are the most cited advantages of minimally invasive surgery (MIS) compared to open surgery [15]. However, minimally invasive techniques, though frequently used in many operations on the digestive tract, are still far from being considered a gold standard. According to data from the National Comprehensive Cancer Network (NCCN) centres, in 2010, the percentage of minimally invasive colorectal resection was about 50% [16]. Percentages for minimally invasive liver surgery are even lower, in a paper published by the American College of Surgeons, in 2014, less than 20% of the liver resections were performed with a MIS [17].

Advantages offered by the robotic platform include a 3D stable camera, instruments with Endowrist technology and better ergonomics for the first surgeon. High costs and longer surgical times are its most important drawbacks [15].

In rectal surgery, the 3D magnificence may aid in preserving nerves with better functional outcomes, in mesorectal excision and in low or ultra-low resections with at least the same postoperative results obtained with laparoscopic surgery with lower conversion rates but longer operative time [10,18,19].

Even in liver surgery, concerns about laparoscopic liver resection have been gradually overcome owing to the emerging benefits offered by the MIS in short-term outcomes with at least similar oncologic outcomes in high-volume centres [20,21]. The robotic platform may aid in bleeding control, biliary and vascular reconstruction, and in posterior segment resections [19]. However, in high-volume hospitals, difficult liver laparoscopic procedures were routinely performed.

b. Aim of the study

During the first year of this project, we performed a comparison between open, laparoscopic and robotic surgery for rectal cancer in terms of short and long-term outcomes finding an important selection bias because, in our reality, open surgery was chosen only in patients affected by cT4 cancer. Consequently, the aim of this final analysis is to perform a further focus comparing laparoscopic and robotic surgery for the treatment of lower rectum cancer in terms of short and long-term outcomes.

For liver surgery, all the interventions requiring a biliary reconstruction were performed with an open technique. During the second year of this project, we performed a comparison between open and MIS for hepatocellular carcinoma in terms of short and medium-term outcomes, consequently, the other aim of this final analysis is to compare open and MIS for the treatment of the first occurrence of liver metastasis in terms of short and long-term outcomes allowing to further analyze the effect of the technique used to resect primary cancer on the treatment of the secondary tumour.

MATERIALS AND METHODS

a. Patients

All the patients undergoing surgery during the study period for rectal cancer or the first occurrence of liver metastasis from colorectal adenocarcinoma were prospectively entered in a dedicated database containing patient information, treatments data, results of the pathological examination, and long-term oncological outcomes. The study period spans from November 2018 to August 2021 to have a minimum of 1 month of follow-up and to conduct the final analysis before the end of the project.

Preoperative data comprehended demographic information, medical history, including the body mass index (BMI), previous abdominal surgery or preoperative chemo or radiotherapy, and the results of the preoperative evaluations.

Routine preoperative assessment included colonoscopy with bioptic essay for rectal cancer; triple-phase contrast-enhanced Computed Tomography of the thorax and the abdomen; pelvic Magnetic Resonance Imaging (MRI) for rectal cancer, or upper abdominal MRI for liver metastasis unless contraindicated; biopsy of liver lesions was required in case of doubtful imaging or when a histological diagnosis was required to start chemotherapy. In selected cases, a Positron Emission Tomography scan was added. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19.9 (CA 19.9) were evaluated mostly in patients with liver metastasis.

Lower rectal cancer was defined if located at 7 cm or less from the anal verge.

Liver metastasis presentation was considered metachronous if occurred at least 3 months later than the diagnosis of the primary tumour.

Indications for the treatment for each patient were given after the Multidisciplinary Team evaluation and followed national and international guidelines. In particular, the patient's conditions (i.e., comorbidities, bowel obstruction), number, dimension and position of the liver metastases at the preoperative examination were taken into account to decide the order of the treatment in case of synchronous presentation.

The kind and the technique of the surgery were chosen by the surgeons having expertise in rectal or liver surgery and both open and MIS.

The patients who did not receive a colorectal anastomosis were excluded from the analysis of rectal cancer.

Major hepatectomies were defined as resection of at least 3 segments according to Brisbane's classification [22].

All patients received prophylactic antibiotic therapy and low-weight molecular heparin to prevent site infections and deep-venous thromboembolism, respectively.

The preoperative planning was confirmed after the exploration of the abdominal cavity and, for liver surgery, after intraoperative ultrasonography evaluation.

For rectal surgery, the operative room set-up is shown in Figure 1.

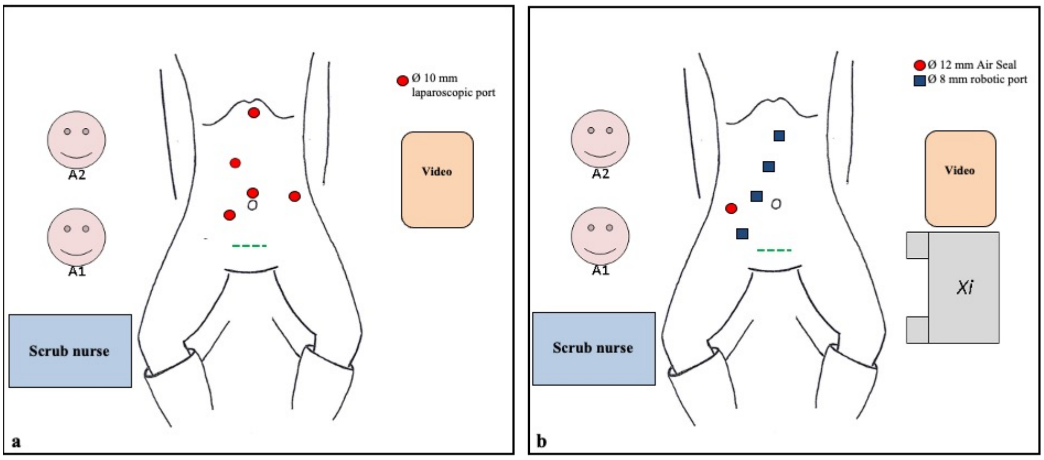

FIGURE 1. Operative room set-up. **a. Laparoscopic technique**. **b. Robotic technique.**
Green dotted line= incision for specimen retrieval.

All the colorectal anastomoses were performed according to the Knight-Griffen technique and all the patients received a diverting loop ileostomy.

For liver surgery, the operative room set-up is represented in Figure 2.

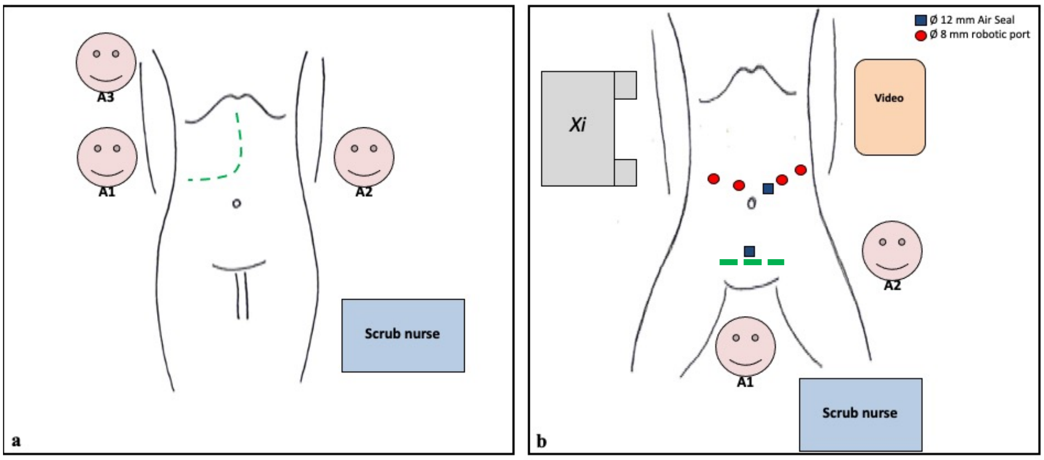

FIGURE 2. Operative room set-up. **a. Open technique**. **b. Robotic/laparoscopic technique.** The hypogastric trocar is used for the Pringle manoeuvre.
Green dotted line= incision line.

Parenchymal transection was performed with the Cavitron Ultrasonic Aspirator (CUSA) for the open and laparoscopic technique or mostly with monopolar scissor and bipolar grasp for the robotic technique.

Perioperative outcomes included details on surgical technique, surgery duration, intraoperative complications and postoperative course. For liver surgery, the (International Normalized Ratio) INR and bilirubin level on postoperative day 5 were evaluated according to the "50-50" criteria [23]. Clavien-Dindo's model was used to classify the postoperative complications [24].

Data about oncological outcomes comprehended histopathological information including circumferential radial margin and quality of mesorectal excision for rectal surgery or margin status for liver surgery and, eventually, time and site of disease relapse.

Mortality was defined as 90-day or in-hospital surgery-related death. The postoperative hospital stay was calculated from the day of surgery to the day of discharge.

For rectal surgery, the disease-free interval was considered as the time between rectal surgery and the diagnosis of any site of recurrence of disease or until the date of death while overall survival was considered as the time between the rectal surgery and the date of death or the last visit for alive patients.

For liver surgery, the disease-free interval was considered as the time between liver surgery or colorectal surgery in case of liver-first treatment and the diagnosis of any site of recurrence of disease or until the date of death while overall survival was considered as the time between the colorectal surgery or liver surgery in case of liver-first treatment and the date of death or the last visit for alive patients. Recurrences were treated with surgery, chemotherapy, radiotherapy, percutaneous treatment, combinations of them or best supportive care, as appropriate.

Follow-up was conducted in a multidisciplinary manner involving surgeons and oncologists. Data were collected from medical files or updated by phone call.

b. Analysis

All data were collected prospectively and reviewed retrospectively.

Patient characteristics, operative and postoperative results, histological findings and long-term oncological outcomes were compared between the patients who underwent laparoscopic versus robotic anterior resection of the rectum and open versus minimally invasive surgery for colorectal liver metastasis.

The analysis was conducted with an “intention-to-treat” aim.

Quantitative data are expressed as mean±standard deviation or median and range (explicitly stated in the table), as appropriate.

Comparisons based on quantitative data were performed using the Student’s t-test or Mann-Whitney test while categorical variables were compared using the χ^2 or Fisher’s exact test.

Statistical significance was defined as p-value <0.05.

Missing data were explicitly mentioned in the tables if they resulted in being more than 10% of the total.

An estimate of DFS and OS rates were calculated according to the Kaplan-Meier methods and compared using the Log-rank test.

All collected information was analysed using the SPSS for Windows 24.0 software package (SPSS Inc, Chicago, Illinois, USA).

RESULTS

a. Rectal surgery

During the study period, 15 patients underwent an anterior resection of the rectum with a contemporary anastomosis for a lower rectal cancer. Eight of them were treated with a laparoscopic technique while the other 7 with a robotic approach. Patient characteristics are shown in Table 1.

Table 1. Patient Characteristics

	Laparoscopy n= 8 (53,3%)	**Robotic surgery** n= 7 (46.7%)	Total n= 15	**p value**
Age (years±SD)	67.1±12	66±14	66.6±13	0.870
Sex (n, %)				0.833
Male	5 (62.5%)	4 (57.1%)	9 (60%)	
Female	3 (37.5%)	3 (42.9%)	6 (40%)	
BMI (±SD)	23.6±4.5	24.5±2.1	24±3.5	0.668
Comorbidities (n, %)				0.833
No	3 (37.5%)	3 (42.9%)	6 (40%)	
Yes	5 (62.5%)	4 (57.1%)	9 (60%)	
Prev abd surgery (n, %)				0.619
No	3 (37.5%)	4 (57.1%)	7 (46.7%)	
Yes	5 (62.5%)	3 (42.9%)	8 (53.3%)	
Symptoms (n, %)				0.919
Bleeding	7 (87.5%)	6 (85.7%)	13 (86.7%)	
Bowel obstruction	1 (12.5%)	1 (14.3%)	2 (13.3%)	
Preop Hemoglobin (g/dL±SD)	13.8±1.7	13.4±1.3	13.2±1.5	0.700
Preop glycemic level (g/dL±SD)	0.98±0.5	1.0±0.2	0.99±0.4	0.902
Preop Creatinine (mg/dL±SD)	0.82±0.2	0.91±0.2	0.87±0.2	0.417
Preop total protein (g/dL±SD)	6.8±0.6	6.7±0.5	6.8±0.5	0.644
NeoadjCHT/RT (n, %)				0.132
No	6 (75%)	2 (28.6%)	8 (53.3%)	
Yes	2 (25%)	5 (71.4%)	7 (46.7%)	

SD= Standard Deviation; BMI= Body mass Index; Prev= Previous; Abd= Abdominal; Preop= Preoperative; CHT/RT= Chemo/radiotherapy treatment

No significant differences were found in patient characteristics. However, the great majority of the patients receiving a neoadjuvant treatment were treated with the robotic technique. Most of them underwent a long-course treatment (45 or 50.4 Gy, fractionated in 25 sessions) associated or not with the radiosensitizer oral capecitabine. A restaging pelvic MRI was always performed. Only one patient did not show at least partial tumour regression.
Operative results are shown in Table 2.

Table 2. Operative results

	Laparoscopy n= 8 (53,3%)	Robotic surgery n= 7 (46.7%)	Total n= 15	p value
Surgery time (min±SD, range)	248.8±38	312.1±55	278±56	**0.021**
Refeeding (POD±SD)	2.9±3.3	2.3±0.5	2.6±2.4	0.650
Bowel function (POD±SD)	1.6±0.7	1.4±0.5	1.5±0.6	0.573
Drain removal (POD±SD)	5.4±1.9	5.7±0.8	5.5±1.5	0.735
NG tube removal (POD±SD)	2±3.2	0.6±0.5	1.3±2.4	0.273
Complications (n, %)				0.833
No	5 (62.5%)	4 (57.1%)	9 (60%)	
Yes	3 (37.5%)	3 (42.9%)	6 (40%)	
Complications CD III-IV (n, %)				0.605
No	6 (75%)	6 (85.7%)	12 (80%)	
Yes	2 (25%)	1 (14.3%)	3 (20%)	
Anastomotic leak (n, %)				0.919
No	7 (87.5%)	6 (85.7%)	13 (86.7%)	
Yes	1 (12.5%)	1 (14.3%)	2 (13.3%)	
Hospital stay (days±SD, range)	7.7±5.8 (5-22)	9.1±8.8 (5-29)	8.4±7	0.720
Readmission (n, %)				0.438
No	7 (87.5%)	5 (71.4%)	12 (80%)	
Yes	1 (12.5%)	2 (28.6%)	3 (20%)	
Stoma reversal (n, %)				0.858
No	2 (40%)	1 (20%)	3 (30%)	
Yes	3 (60%)	4 (80%)	7 (70%)	
Waiting	3	2	5	

NG tube= Nasogastric tube; CD III - IV = Clavien-Dindo Classification grade III - IV; CHT = Chemotherapy

Global conversion to open surgery rate was 6.7% and only one patient required conversion from the laparoscopic technique for the mesorectal step because of the huge burden of disease (conversion rate for the laparoscopic group of 12.5%, not shown in the table).

Surgery time was significantly longer for the robotic technique, but it did not translate into higher morbidity rates (20% considering only severe complications).

Postoperative complications included 2 episodes of subocclusion (1 occurring after discharge and requiring readmission), a chyloperitoneum, 1 jejunal perforation and 2 anastomotic leaks (AL), the last 3 required a reintervention (jejunal resection and two Hartmann's procedures). Since all the patients received a diverting loop ileostomy, those experiencing an AL were initially treated with conservative management but subsequently required readmission because of AL persistence.

Three patients will never get the stoma reversal, two because they underwent the Hartmann's procedure after the anastomotic leak and one because of disease progression. There are 5 patients still awaiting stoma reversal, one of them experienced anastomotic stenosis which required multiple dilatations.

Pathological results and oncological outcomes are shown in Table 3.

Table 3. Pathological results and other oncological outcomes

	Laparoscopy n= 8 (53,3%)	Robotic surgery n= 7 (46.7%)	Total n= 15	p value
Length of the specimen (cm±SD)	25.1±5.4	23.6±3.7	24.4±4.6	0.537
Size (mm±SD)	49.4±17.6	14±15	32.9±24.2	**0.001**
T stage (n, %)				**0.012**
0-1	0	5 (71.4%)	5 (33.3%)	
2	2 (25%)	2 (28.6%)	4 (26.7%)	
3	6 (75%)	0	6 (40%)	
Nodes harvested (n±SD)	33.6±14.9	15.7±9.2	25.3±15.3	**0.017**
Positive nodes (n±SD)	0.6±1.8	0	0.3±1.3	0.369
Distal margin (mm±SD)	1.8±1.1	2.1±0.8	1.9±0.9	0.692
CRM (mm±SD)	1.1±0.7	2.2±0.5	1.6±0.8	**0.015**
Mesorectal excision quality (n±SD)				0.427
Incomplete	0	1 (14.3%)	1 (6.7%)	
Nearly complete	2 (28.6%)	3 (42.9%)	5 (33.3%)	
Complete	5 (71.4%)	3 (42.9%)	8 (53.3%)	
Adjuvant CHT (n, %)				**0.026**
No	3 (37.5%)	7 (100%)	10 (66.7%)	
Yes	5 (62.5%)	0	5 (33.3%)	
Recurrence (n, %)				0.200
No	5 (62.5%)	7 (100%)	12 (80%)	
Yes	3 (37.5%)	0%	3 (20%)	

T stage according to TNM definition AJCC 8th edition.

The specimens from the patients treated with the robotic technique presented with significantly smaller tumours, lower T stage, lower number of nodes harvested (but with a mean above the required number of 12), wider CMR.

Patients started chemotherapy within a mean of 70 days (±27). Only patients treated with a laparoscopic technique received chemotherapy, thus precluding further analysis.

All the patients are alive. With a median follow-up of 14 months (7-33 months), three patients experienced disease recurrence, all treated with a laparoscopic technique. Estimated mean DFS was 25.3 months (95% Confidence Interval [95%

CI] 18-32). No differences in DFS were found between the two techniques (p=0.165). Sites of recurrence were the liver, the pelvic peritoneum, and anastomosis.

One of the 3 patients experiencing recurrence, was actually cured and disease-free after a Miles procedure for anastomotic recurrence of the disease.

b. Liver surgery for colorectal metastasis

During the study period, 51 patients underwent surgery for the first occurrence of liver metastasis from colorectal adenocarcinoma. Fifty of them were treated with an open technique while 10 with a minimally invasive approach (6 laparoscopically assisted and 4 robotic-assisted). One patient died because of a stroke within 15 days from surgery and she was excluded from the final analysis.

Patient characteristics are shown in Table 4.

Table 4. Patient Characteristics

	Open n=40 (80%)	MIS n=10 (20%)	Total n= 50	p value
Age (years,±SD)	61 ±13	62±8	61.6±12	0.839
BMI (±SD)	25±4	25±6	25.3±4.3	0.978
Sex (n, %)				0.382
Male	26 (65%)	5 (50%)	31 (62%)	
Female	14 (35%)	5 (50%)	19 (38%)	
Smoke habit (n, %)				0.721
No	26 (66.7%)	6 (60%)	32 (65.3%)	
Yes	13 (33.3%)	4 (40%)	17 (34.7%)	
Comorbidities (n, %)				0.567
No	16 (40%)	5 (50%)	21 (42%)	
Yes	24 (60%)	5 (50%)	29 (58%)	
ASA (n, %)				0.307
1	1 (2.5%)	1 (10%)	2 (4%)	
2	29 (72.5%)	5 (50%)	34 (68%)	
3	10 (25%)	4 (40%)	14 (28%)	
Previous abdominal surgery (n, %)				0.563
No	7 (17.5%)	1 (10%)	8 (16%)	
Yes	33 (82.5%)	9 (90%)	42 (84%)	
Preoperative Hemoglobin (g/dL)	12.9±2	14±1.3	13.1±2	0.78
Preoperative Creatinine (mg/dL)	0.81±0.2	0.81±0.2	0.81±0.19	0.839
Preoperative bilirubin (mg/dL)	0.5±0.3	0.7±0.4	0.5±0.3	0.184
Maximum preoperative CEA (ng/mL; median, range)	13 (1.6-337.9)	23 (3-439.6)	17	0.120
RT/CHT before liver surgery (n, %)				0.083
No	9 (22.5%)	5 (50%)	14 (28%)	
Yes	31 (77.5%)	5 (50%)	36 (72%)	

MIS= Minimally invasive surgery; ASA = American Society of Anaesthesiologists; CEA= Carcinoembryonic antigen; RT/CHT= include radiotherapy (associated or not with capecitabine) and/or chemotherapy

No significant differences were found in patient characteristics. However, a greater number of the patients receiving medical treatment before liver surgery were treated with the open technique.

The great majority of the patients were treated, eventually within clinical trials, with the triplet FOLFOX (folinic acid, fluorouracil, and oxaliplatin) or with the quadruplet FOLFOXIRI (folinic acid, fluorouracil, oxaliplatin, and irinotecan). Furthermore, most of them received a biological agent (i.e. cetuximab, bevacizumab, or panitumumab). A restaging imaging (CT scan and/or MRI) was always performed, at least stable disease was required to proceed to surgery, except for selected patients experiencing disease progression (but still resectable) and deemed not fit for further lines of medical treatment.

Tumour characteristics are shown in Table 5.

Table 5. Tumour Characteristics

	Open n=40 (80%)	**MIS** n=10 (20%)	Total n= 50	**p value**
Site of the primary tumour (n, %)				0.201
Right colon	8 (20.5%)	3 (30%)	11 (22.4%)	
Left colon	20 (51.3%)	2 (20%)	22 (44.9%)	
Rectum	11 (28.2%)	5 (50%)	16 (32.7%)	
Technique for primary tumour (n, %)				
Minimally invasive	21 (56.8%)	8 (80%)	29 (61.7%)	0.336
MIS Converted to open	4 (10.8%)	0	4 (8.5%)	
Open	12 (32.4%)	2 (20%)	14 (29.8%)	
Metastasis presentation (n, %)				0.528
Metachronous	15 (37.5%)	6 (60%)	21 (42%)	
Synchronous, bowel-first	12 (30%)	1 (10%)	13 (26%)	
Synchronous, liver-first	9 (22.5%)	2 (20%)	11 (22%)	
Synchronous, combined	4 (10%)	1 (10%)	5 (10%)	
Number of lesions (n±SD)	3.9±3	1.9±2	3.5±3	**0.046**
Maximum diameter (mm±SD)	33±22	29.8±12	32.4±20	0.654
"Laparoscopic segments" only (n, %)				0.197
No	33 (82.5%)	6 (60%)	39 (78%)	
Yes	7 (17.5%)	4 (40%)	11 (22%)	

MIS= Minimally invasive surgery

One patient was treated for lung and liver metastasis from colorectal cancer but the site of the primary tumour is still unknown. The other two patients did not undergo surgery for their primary tumours because of disease progression.
Analysing the data from the preoperative imaging, the number of liver lesions was significantly higher in the open group while there is a trend in a higher number of metastases located only in the so-called laparoscopic segments for the MIS group. The operative results are shown in Table 6.

Table 6. Operative results

	Open n=40 (80%)	**MIS** n=10 (20%)	Total n= 50	**p value**
Type of surgery (n, %)				0.178
Major	18 (45%)	2 (20%)	20 (40%)	
Minor	15 (37.5%)	7 (70%)	22 (44%)	
Multiple wedges	7 (17.5%)	1 (10%)	8 (16%)	
Pringle manoeuvre (n, %)				**0.014**
No	12 (30%)	8 (80%)	20 (40%)	
Yes	28 (70%)	2 (20%)	30 (60%)	
Number of manoeuvres	1.4±1	1.2±2.5	1.34±1.7	0.769
Maximum length (min±SD)	8.8±7	4.3±9	7.8±8	0.116
Total length (min±SD)	18.8±18	24.7±44	20.1±25.4	0.525
Hanging manoeuvre (n, %)				0.279
No	22 (55%)	8 (80%)	30 (60%)	
Yes	18 (45%)	2 (20%)	20 (40%)	
Vascular resection (n, %)				0.372
No	37 (92.5%)	10 (100%)	47 (94%)	
Yes	3 (7.5%)	0	3 (6%)	
Intraoperative complications (n, %)				0.616
No	35 (87.5%)	8 (80%)	43 (86%)	
Yes	5 (12.5%)	2 (20%)	7 (14%)	
Surgery time (min; median, range)	291 (113-485)	318 (163-741)	297.5	0.458

MIS= Minimally invasive surgery; Minor = Minor hepatectomies/hepatic wedge resections (up to 2); Major= Major hepatectomies; Multiple wedges = At least 3 wedges

Conversion to open surgery rate was 10% and only one patient required conversion from the laparoscopic technique because of a high grade of liver steatosis.

Although not significant, patients needing a major resection were more frequently treated with the open technique. Surgery time was similar but the different distribution of the kind of surgery has to be taken into account. The patient undergoing the longest operation had both the primary and the metastasis resected. The Pringle manoeuvre was more frequently used with the open technique.

Intraoperative complications included 3 respiratory, 3 vascular, and 1 biliary complication.

Table 7 shows the postoperative results.

Table 7. Postoperative results

	Open **n=40 (80%)**	**MIS** **n=10 (20%)**	Total n= 50	**p value**
ICU				0.331
No	5 (12.5%)	3 (30%)	8 (16%)	
Yes	35 (87.5%)	7 (70%)	42 (84%)	
INR POD 5 (±SD)	1.1±0.1	1.1±0.1	1.1±0.1	0.486
Total Bilirubin POD 5 (mg/dL±SD)	1.1±0.7	0.9±0.6	1.1±0.7	0.589
Refeeding (POD±SD)	2.2±1.3	2.2±1.5	2.2±1.3	0.966
Bowel function (POD±SD)	4.4±1.5	4.2±1.3	4.4±1.5	0.700
Drain removal (POD±SD)	5.3±2.8	3.5±1.8	4.9±2.7	0.099
Complications				**0.010**
No	23 (57.5%)	10 (100%)	33 (66%)	
Yes	17 (42.5%)	0	17 (34%)	
Length of hospital stay (days±SD)	8.5±4.4	4.7±2.3	7.7±4.3	**0.012**
Need for blood transfusion (n, %)				0.416
No	29 (72.5%)	9 (90%)	38 (76%)	
Yes	11 (27.5%)	1 (10%)	12 (24%)	
Readmission				0.327
No	34 (85%)	10 (100%)	44 (88%)	
Yes	6 (15%)	0	6 (12%)	

MIS= Minimally invasive surgery; ICU= Intensive Care Unit; INR= International Normalized Ratio; POD= Postoperative day; CD III - IV = Clavien-Dindo Classification grade III - IV; CHT = Chemotherapy

Mild complications included perihepatic fluid collections, mild and transient postoperative liver failure, chylous ascites, or surgical site infection; severe complications included biliary leak or pleural effusion causing respiratory distress needing a percutaneous drain (some of them appeared after discharge thus requiring readmission). Only one patient experiencing a high-flow biliary leak required a redo-surgery (right hepatectomy) after multiple wedge resections.

The global number of postoperative complications was significantly higher in the open group and severe complications were reported only for the open group (8 patients, 16% of the global series and half of the complication occurred).

Hospital stay was significantly lower in the MIS group.

Pathological results and oncological outcomes are shown in Table 8.

Table 8. Pathological results and other oncological outcomes

	Open n=40 (80%)	**MIS** n=10 (20%)	Total n= 50	**p value**
Resected lesions (n±SD, range)	2.6±1.9	1.3±0.7	2.3±1.8	**0.063**
Maximum Size (mm; median, range)	27.7	15	29	0.676
Margin (n, %)				0.363
No	39 (97.5%)	9 (90%)	48 (96%)	
Yes	1 (2.5%)	1 (10%)	2 (4%)	
KRAS mutation				0.434
No	19 (54.3%)	6 (75%)	25 (58.1%)	
Yes	16 (47.5%)	2 (25%)	18 (41.9%)	
Missing	5	2	7	
Other molecular mutation				0.171
No	26 (74.3%)	8 (100%)	34 (79.1%)	
Yes	9 (25.7%)	0	9 (20.9%)	
Missing	5	2	7	
CHT after liver surgery (n, %)				0.720
No	16 (41%)	3 (30%)	19 (38.8%)	
Yes	23 (59%)	7 (70%)	30 (61.2%)	
Time to start CHT (days±SD)	68.3±37	61.5±15	66.5±32	0.668
Recurrence (n, %)				0.171
No	14 (35%)	6 (60%)	20 (40%)	
Yes	26 (65%)	4 (40%)	30 (60%)	

MIS= Minimally invasive surgery

No significant differences were found in the results of the pathological specimen analysis. However, the number of resected lesions approached significance. The global positive margin rate was 4%.

The regimens used for adjuvant chemotherapy were the same as those used before liver surgery unless disease progression. The time to start chemotherapy was similar.

The most frequent sites of recurrence were liver followed by lung, perianastomotic site and peritoneum.

Five of the 30 patients experiencing recurrence (all treated with an open liver surgery), were actually cured and disease-free after further treatments (chemotherapy and surgical resection).

Analysing the initial group of 51 patients, postoperative mortality was 2%.

With a median follow-up of 25 months (1-52 months), the estimated mean OS was 46 months (95% CI 42-50). All the dead patients were treated with an open technique, thus precluding further comparative analysis. The estimated mean and median DFS were 22 months (95% CI 15,6-29) and 8 months, respectively.

Figure 3 shows the Kaplan-Meier curve of DFS stratified by technique.

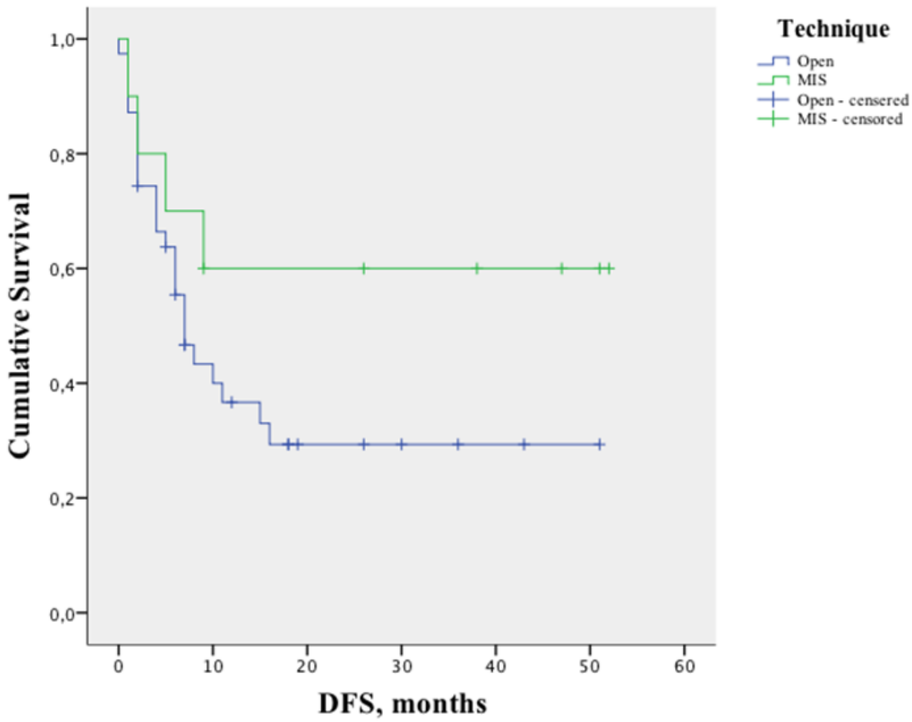

FIGURE 3. Kaplan–Meier curve of disease-free survival (DFS) (p=0.164) stratified by Technique of liver resection.

Open = Open surgery approach - MIS = Minimally invasive surgery including robotic and laparoscopic technique - CI= Confidence Interval

Performing a further analysis stratifying for the number of lesions (1-2 vs 3 or more), no significant differences were found in the DFS (Figure 4).

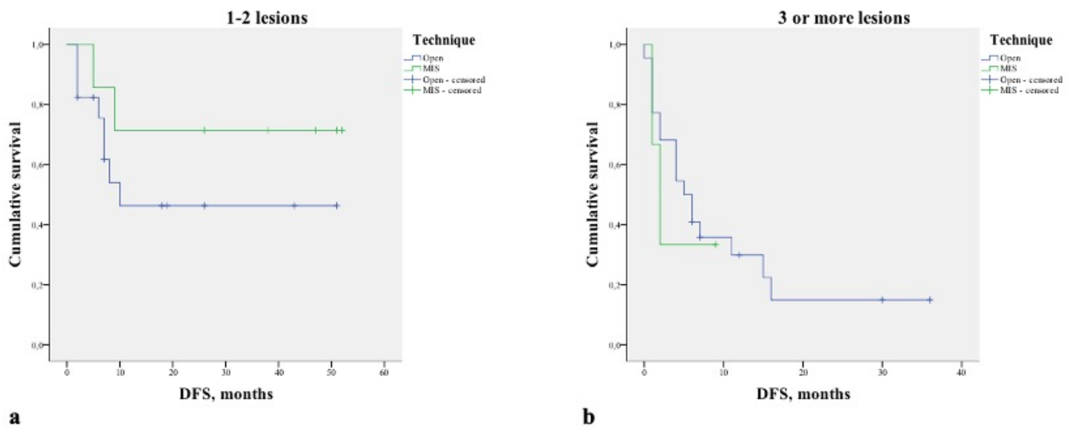

FIGURE 4. Kaplan–Meier curve of disease-free survival (DFS) (p=0.527) stratified by the preoperative number of resected lesions. **a. 1-2 lesions**. Mean DFS rates for Open and MIS were 26.7 months ±6 and 39.1 months ±7.7, respectively. **b. 3 or more lesions.** Mean DFS rates for Open and MIS were 10.4 months ±2.7 and 4 months ±2, respectively.

Open = Open surgery approach - MIS = Minimally invasive surgery including robotic and laparoscopic technique

Similarly, no differences were found stratifying the analysis for the technique used to treat primary cancer (p=0.148), margin status (p=0.153), and KRAS mutation (p=0.735) (Figure 5).

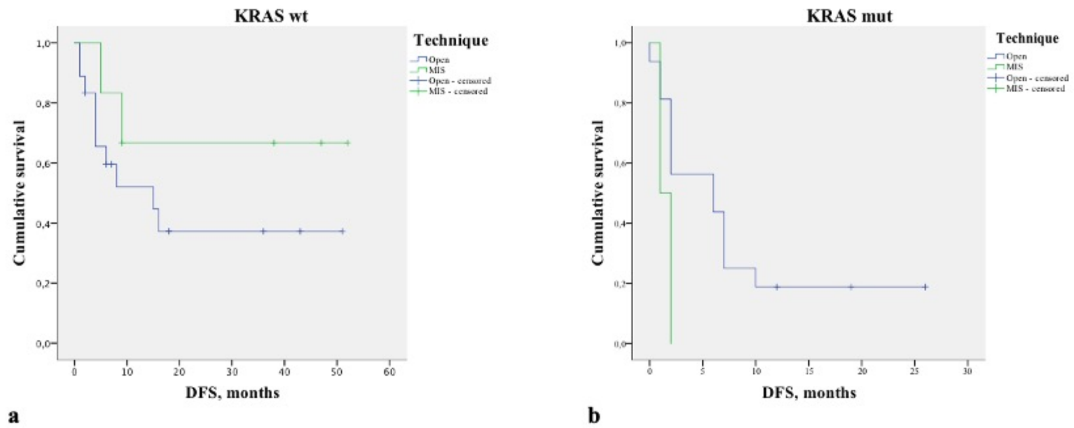

FIGURE 5. Kaplan–Meier curve of disease-free survival (DFS) (p=0.735) stratified by KRAS status. **a. KRAS wild-type**. Mean DFS rates for Open and MIS were 23.2 months ±5.6 and 37 months ±8.7, respectively. **b. KRAS mutation.** Mean DFS rates for Open and MIS were 8.2 months ±2.2 and 1.5 months ±0.5, respectively.

Open = Open surgery approach - MIS = Minimally invasive surgery including robotic and laparoscopic technique

DISCUSSION

The present study reports our experience with two selected cohorts of patients, those affected by lower rectal cancer and those experiencing the first occurrence of colorectal adenocarcinoma liver metastasis during a 3-years time period.

Colorectal cancer has a high incidence, but it has also a quite high potential cure rate compared to other tumours, even in the metastatic setting. Within a multimodal approach involving perioperative chemotherapy, radiotherapy or chemoradiotherapy treatments, surgery has a key role in the cure of the patients.

While there are several papers about the results of the different techniques used in colon surgery, fewer data are available about open or laparoscopic rectal surgery [25,26]. Some multicentric prospective randomized trials, including the CLASICC or the COLORS II, reported the superiority of laparoscopy over open surgery for rectal cancer in terms of short-term outcomes [26,27]. Despite a higher number of involved circumferential resection margin (CRM) in the laparoscopic group of the CLASICC trial, no differences were found in the local recurrence rate at 3 and 5-years of follow-up [26]. Further studies reported the same pathological results, similar overall survival (OS) and disease-free survival (DFS) rates with better preservation of the quality of life for laparoscopic surgery compared to open surgery [19,27,28]. On the contrary, as always happens in Literature, two large randomized trials, the ALaCaRT and the ACOSOG concluded that the evidence was not sufficient to support the routine use of the laparoscopic technique [29,30].

In the early 1990s, robotic-assisted laparoscopic surgery was introduced into clinical practice providing some technical advantages over the difficulties of laparoscopic surgery. During the following years, several reviews, meta-analyses, and some randomized control trials, including the ROLARR study, were published demonstrating no clear advantage for robotic over laparoscopic surgery in terms of short-term outcomes and pathological results, with a trend in lower conversion rates (mostly in males) and probable better preservation of the urinary and sexual quality of life for the robotic group [10,31–33]. Similarly, no obvious advantages in the OS, the DFS or the local recurrence rates were found after robotic surgery compared to the laparoscopic technique [33,34].

The reported conversion rate for laparoscopic surgery ranged between 9% and 34% while it is reported to be about 10% in robotic surgery [26,29,30,33]. In our series, the conversion rates for laparoscopic and robotic groups were 12.5% and 0%, respectively. Possible explanations include: first, the small sample size analysed may be not sufficient to observe more events; second, advanced tumours presenting with a more difficult dissection plane are preferably treated without an anastomosis (Hartmann's procedure) or directly with an open technique.

For robotic surgery, surgery duration is one of the most cited drawbacks [33]. The first part of the learning curve of the console surgeon and assistant surgeon is one of the potential reasons advocated for the longer surgery time and expertise in robotic surgery seems more important than the experience with laparoscopy [33]. However, in this study, both the console surgeon and the assistant surgeon could be considered to be at the plateau of their learning curve in robotic surgery.

In this study, the morbidity rate was 40% (20% if considering severe complications only). In particular, 2 anastomotic leaks were reported (13.3%). Anyhow, since patients received a diverting loop ileostomy, this rate could be underestimated. Similarly, the reported 30-days morbidity rate is about 30% [33]. The introduction of robotic staplers could improve the rectal section and, consequently, colorectal anastomosis. However, since robotic stapler use requires a specific bigger trocar, and the costs are higher, only manual staplers were used in this case series.

Globally, the positive CRM rate was 0% while the complete mesorectal excision rate was 53.3%. The reported positive CRM ranged between 6% and 12% while a complete mesorectal excision was reported in 76-88% of the patients [26,29,30,33]. As previously stated, the small number of patients analysed could explain these differences. Furthermore, for these parameters, the expertise of the pathologists and the not always adherence to a rigorous standardization could also cause a bias.

As in the previously cited papers, we did not find a clear superiority of the robotic technique over laparoscopy in the pathological results. The specimens from the patients treated with the robotic technique presented with significantly smaller tumours, lower T stage, lower number of nodes harvested (although above the number of 12 which is required for a correct stadiation), similar quality of mesorectal excision, and wider CMR. These results may be related to the higher number of patients receiving neoadjuvant treatments in the robotic group. Radiotherapy is usually associated with more challenging dissection planes, at least partially explaining the presence of one incomplete mesorectal excision and the longer surgery time in the robotic group. Furthermore, since we observed a tumour regression grade up to 100%, this could explain the smaller tumour size and T stage observed in the robotic group. Consistently, a greater number of the patients of the laparoscopic group received adjuvant chemotherapy.

Interestingly, Park et al. performed a retrospective single-centre propensity score-matched analysis on mid-low rectal cancers reporting a significant DFS benefit after robotic surgery in the subset of more advanced rectal cancer who received neoadjuvant treatments (ypT3-4) [35].

Furthermore, Nagtegaal et al. found a significantly higher predictive value of the CRM for disease recurrence in the patients receiving neoadjuvant treatments [36].

An analysis of the urinary and sexual quality of life is needed together with the cost-effectiveness analysis. However, cost analysis should also consider the emerging aspect of work-related musculoskeletal disorder potentially affecting surgeons [37].

The robotic platform could provide a better ergonomic at least to the console surgeon.

The first laparoscopic hepatectomies were reported in the 1990s [38]. The Louisville statement in 2008 represented a try to standardize the surgical practice. However, from the Louisville statement to the Southampton statement in 2017, passing through the Morioka statement in 2014, indications for MIS have been widened [14,39,40]. Initially, MIS was only indicated to treat solitary lesions, smaller than 5 cm, and located in segments 2 to 6 (the anterolateral segments or the so-called laparoscopic segments), major resections should be performed only by experienced surgeons [39]. The Morioka statement focused on the comparison with open surgery trying to demonstrate the non-inferiority of the MIS [40]. The last statement moved toward emphasizing the benefits of MIS over open surgery and tried to promote MIS safe implementation with the appropriate expertise [14]. Older ages, high BMI, previously liver resections, combined resection of the primary and metastatic disease or complex resections near pedicles or in the posterosuperior segments (1, 4a, 7, and 8) are no more contraindications to MIS in experienced hands [14,41]. Up to 70% of the patients with colorectal liver metastasis could be a candidate for MIS in high-volume centres [42].

Several papers including reviews, meta-analyses and also the randomized controlled trial OSLO-COMET, suggested reduced intraoperative blood loss, lower morbidity rates, and shorter length of hospital stay for MIS compared to open surgery for colorectal liver metastasis [14,21,43–45]. Furthermore, there is growing evidence of at least non-inferiority of MIS in terms of R0 resections, tumour recurrence, OS, and DFS [14,21,43–45].

In 2003, Giulianotti et al. [46] reported their first experiences in robotic liver resections. Although demonstrating a faster expansion together with good safety and feasibility profile [47], even in this case, a real superiority in resective surgery of the robotic approach over laparoscopy was not widely demonstrated yet, also for the resection in the posterosuperior segments [14,48,49]. The higher costs and the longer operative time are again the most frequently cited drawbacks. However, the robotic platform may shorten the learning curve allowing good results even in lower volume centers [47].

In this series, MIS was chosen for patients with a significantly lower number of lesions and with a higher (but not significant) percentage of location in the anterolateral segments only. Our hospital is a medium volume centre, it is expected that with the increase of the activity, more complex resections could be accomplished with a minimally invasive approach. On the contrary, the quite high percentage of the open technique used to treat the primary tumour reflect the fact that some of these patients were referred to our Institute after primary cancer resection.

In this series, minor and non-anatomical resections were performed in the majority of the patients with higher (but not significant) percentages in the MIS group. Unlike hepatocellular hepatocarcinoma, for colorectal metastasis parenchymal sparing surgery seems to be preferable to anatomic resection, whenever possible [14,50–52]. Since colorectal metastasis could be considered as a kind of chronic disease, preserving more parenchyma may allow further resections [44].

During open surgery, significantly greater use of the Pringle manoeuvre was found. Intermittent Pringle manoeuvres or continuous hemi-hepatic inflow control do not impair liver function, it could be used if necessary but it is not mandatory [14,53].

Only patients treated with the open technique experienced postoperative complications and the global morbidity rate was 42.5%. Reported postoperative morbidity rates are about 23% and 44% for MIS and open surgery, respectively [44].

Interestingly, an inverse correlation between morbidity and survival has been proposed. Possible explanations include a prolonged phase of immunosuppression and a delayed start of chemotherapy [54,55].

Consistently, similarly to the previously cited papers, the length of hospital stay was significantly lower in the MIS group in our series.

Our pathological results reported a global R1 resection rate of 4% (2.5% and 10% for the open and the MIS group, respectively). Conversely, reported positive margin rates were 7% and 25% for MIS and open surgery, respectively [44]. The surgical status margin is an important prognostic factor for disease recurrence [56,57]. A margin width of 1 mm seems sufficient to ensure good DFS rates while wider margins do not confer a greater survival benefit [56]. The implementation of the use of the intraoperative ultrasound evaluation over recent years allows for higher R0 rates [44].

The majority of our patients received a perioperative chemotherapy treatment, generally platinum-based, and most of them were also treated with biological drugs. Perioperative chemotherapy may allow for a prolonged DFS in both the setting of resectable or upfront unresectable disease [58]. However, potential hepatotoxicity derived from chemotherapy (mostly platinum-related sinusoidal obstruction syndrome) has to be taken into account when evaluating liver resection extension to reduce the risk of post-hepatectomy liver failure. On the contrary, the inhibitor of the vascular endothelial growth factor bevacizumab seems to protect the liver from this damage [59].

This study has some limitations. It is a retrospective study with an inherent selection bias. The two series are quite small, and this should lead to a careful and critical interpretation of some findings. Nevertheless, the small number of patients analysed precluded a propensity score-matched analysis that could add value to the results, mostly in the liver cohort. Some missing data may also cause bias throughout the analysis. The follow-up period is quite short due to the study period span, consequently, further longer-term analyses are required.

CONCLUSIONS

Evidence from these analyses is too weak to give any real recommendation.

For rectal surgery, similarly to the previously reported evidence, we failed to demonstrate a clear superiority of the robotic technique over laparoscopy. However, we can conclude that in difficult cases, including patients with higher BMI and those who received neoadjuvant treatment, the robotic technique may allow at least similar or better oncological results compared to laparoscopy. A cost-effective analysis is required but it should also take into account the potential costs associated with the surgeon's work-related musculoskeletal disorders which are receiving greater attention during the last years.

For liver surgery, MIS and parenchymal sparing resections should be preferred whenever technically feasible providing better short-term outcomes and similar oncologic results compared to open surgery and more extended resections. The expertise and the multidisciplinary evaluation are of paramount importance to provide the patients with the best treatment. Since a randomized controlled trial could be difficult at the ethical level, bigger numbers are required to perform at least a propensity-score matched analysis.

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