Aldo Rocca (Orcid ID: 0000-0003-3807-3865)

Fabio Carbone (Orcid ID: 0000-0003-4743-7181)

Robotic surgery for colorectal liver metastases resection: a systematic review

Aldo Rocca[1] AR, Andrea Scacchi[1] AS°, Micaela Cappuccio[1] MC°, Pasquale Avella[1] PA, Walter Bugiantella[2] WB, Michele De Rosa[3] MDR, Gianluca Costa[4] GC, Andrea Polistena[5] AP, Massimo Codacci-Pisanelli[5] MCP, Bruno Amato[6] BA, Fabio Carbone[7] *FC, and Graziano Ceccarelli MD, PhD[2] GC

1. Department of Medicine and Health Sciences "V. Tiberio", University of Molise, Via Francesco de Sanctis 1, 86100, Campobasso, Italy. aldo.rocca@unimol.it, micaelacappuccio24@gmail.com, scacchiandrea@me.com, avella.p@libero.it
2. General Surgery, "San Giovanni Battista" Hospital, USL Umbria 2, Via Massimo Arcamone 1, 06034, Foligno, Italy; wbugiantella@alice.it, g.cecca2003@libero.it;
3. Department of General Surgery, 'San Giovanni Battista' Hospital, Perugia, Italy; morrisey1759@hotmail.it.
4. Department of Medical and Surgical Sciences and Translational Medicine, Faculty of Medicine and Psychology, St Andrea Hospital, Sapienza University, Rome, Italy; gianlucacostaphd@gmail.com
5. UOC General Surgery and Laparoscopic Surgery, Department of Surgery "P. Valdoni", Sapienza, University of Study of Rome, University Policlinic Umberto I, Rome, Italy; apolis@yahoo.it, massimo.codacci@gmail.com
6. Department of Public Health, University of Naples "Federico II", Via S. Pansini, 5, 80131 Naples, Italy; bruno.amato@unina.it
7. Department of Advanced Biomedical Sciences, Università di Napoli - "Federico II", Corso Umberto I 40, 80138, Naples, Italy; fa.carbone87@gmail.com;

° Andrea Scacchi e Micaela Cappuccio have equally contributed to the paper.

* **Correspondence to:**
Fabio Carbone,
Department of Advanced Biomedical Sciences, Università di Napoli - "Federico II",
Corso Umberto I 40, 80138, Naples, Italy;
E-mail: fa.carbone87@gmail.com;
Tel: +0039 333 7470706

Author Contributions:

Conceptualization: Aldo Rocca, Fabio Carbone, Graziano Ceccarelli, Bruno Amato

Methodology: Aldo Rocca, Fabio Carbone, Graziano Ceccarelli, Andrea Scacchi, Bruno Amato, Micaela Cappuccio

Writing: Aldo Rocca, Fabio Carbone, Graziano Ceccarelli, Micaela Cappuccio, Andrea Scacchi, Pasquale Avella, Bruno Amato

Writing - review and editing: Aldo Rocca, Fabio Carbone, Graziano Ceccarelli, Andrea Scacchi, Pasquale Avella

Supervision: All authors;

Formal analysis and investigation: Fabio Carbone, Andrea Scacchi, Pasquale Avella, Walter Bugiantella, Michele De Rosa, Gianluca Costa, Andrea Polistena, Massimo Codacci-Pisanelli

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ABSTRACT:

Background: The role of robotic surgery for colorectal cancer liver metastases (CRCLMs) has never been investigated in large series.

Methods: A systematic literature review was carried out on PubMed and Cochrane libraries.

Results: We selected 9 studies between 2008 to 2021. 262 patients were included. 131 patients underwent simultaneous resections. The mean blood loss was 309.4 ml (range, 200-450 ml), the mean operative time was 250.5 min (range, 198.5-449.0 min). The mean length of hospital stay was 7.98 days (range, 4.5 to 12 days). The overall postoperative mortality was 0.4%. The overall morbidity rate was 37.0%, Clavien-Dindo grade III-IV complications were 8.4%. The mean 3-year overall survival was 55.25% (range, 44.4-66.1%), the mean 3-year disease free survival was 37% (range, 33.3-41.9%).

Conclusion: We can conclude that robotic-assisted surgery might be considered as a technical upgrade option for minimally invasive approach to CRCLM resections even for simultaneous operations and challenging cases.

Keywords: colorectal liver metastases; robotic surgery; systematic review

INTRODUCTION

Colorectal Cancer (CRC) is the third most frequent cancer worldwide regarding incidence and the fourth big killer regarding mortality [1]. 50% of patients affected by CRC will develop liver metastasis from diagnosis [2]. Although oncologic therapies have made significant advances, the most effective treatment for Colorectal Cancer Liver Metastasis (CRCLMs) remains surgical resection [3-5].

In the last fifteen years the opportunity to perform of Minimally Invasive (MI) liver resections has been extensively investigated and its rules were clearly stated during the international consensus held in Louisville 2008, Morioka 2014, and Southampton 2017 [6-8].

Despite laparoscopy is still the predominant MI surgical technique to perform liver resections, Robotic Liver Resections (RLR) have been proposed as an alternative approach to overcome some technical limitations of Laparoscopic

Liver Resections (LLR). It has been reported that robotic approach may offer a safer and more comfortable technology than conventional LLR, especially in major and postero-superior segments and complex reconstructive time [9,10]. Although CRCLMs represent a heterogeneous clinical scenario, a dedicate research interest including multicenter experiences and clinical trials are even more necessary to outline the best indication for clinical practice [11-13].

So, accordingly, to the development of surgical technologies and the effectiveness of multimodal therapies also the approach to CRCLMs resection changed both for simultaneous and delayed procedures [3,4,7,10,14-18].

Despite some recent reviews tried to investigate the role of RLR for CRLMs, so far, indications and limits of RLR for CRLMs has not been clearly investigated [19,20].

To date, there are in the literature cases series and meta-analyses that compare RLR and LLR, but these are often heterogeneous regarding surgical indications and they often included a small sample size of patients [6,10,15,21]. This systematic review aims to assess and clarify the safety and oncological outcomes of the robotic resection of CRCLM through a complete and systematic review of the literature.

MATERIAL AND METHODS

Aims

Our primary endpoint is to evaluate the safety of RLR for CRCLMs in terms of postoperative morbidity and mortality. The secondary endpoints are the evaluation of the oncological outcomes, the assessment of the oncological radicality, long-term overall survival (OS) and disease-free survival (DFS) outcomes. The comparison with these results with the current literature can provide an overview of the advantages and disadvantages of the robotic-assisted technique for CRCLMs resection compared with OLR and LLR.

Literature research

A systematic literature review was carried out on PubMed (Medline) and Cochrane libraries on the 23rd of April 2021, taking into consideration all the articles published in the English language without restrictions of time.

The research query was as follow: (robot* OR robotic* OR Vinci) AND (liver OR hepatic* OR hepatectom*) AND (colon* OR colorectal OR rect* OR metastas*). The query keywords were searched in the titles and abstracts.

Inclusion and exclusion criteria

The inclusion criteria were as follow: 1. Original articles with a retrospective or prospective case series of more than three RLR performed for CRCLMs; 2. Studies with at least one of the following outcomes: postoperative morbidity, postoperative mortality, radicality of the surgery (R0/R1-2), overall survival rate, disease-free survival rate.

The exclusion criteria were: 1. RLRs performed for other pathologies except for CRCLM; 2. Case reports, reviews, meta-analysis, letters and editorials; 2. articles that do not have well defined any of the outcomes indicated in the inclusion criteria; 3. Full-text articles not in the English language.

Article screening and selection

All the articles were screened for the inclusion and exclusion criteria by two authors (FC, AS) and incongruences were solved by mutual discussion or querying to a third researcher (AR). The articles eligible for a full-text evaluation were then further screened to select only the articles that fully met the inclusion and exclusion criteria. The screening and review process was carried out in accordance with the PRISMA 2020 statement [22].

Data extraction and processing

The following data were extracted from the selected articles: total number of patients involved, number of patients who underwent RLR with CRCLMs indication, baseline characteristics (age, gender, BMI, ASA score), the total number of liver resections, number of patients undergone to major and minor hepatic resections, number of patients undergoing simultaneous resection procedures with the primary tumor, intraoperative characteristics (blood loss, operative time, use of the Pringle maneuver), postoperative characteristics (30-days mortality, 30-days in-hospital morbidity and major complications, length of hospital stay), follow-up characteristics (radicality of the resections, overall survival, disease-free survival). Complications were classified according to Clavien-Dindo [23]. In the series with an individual description of the results, the data were processed and calculated with SPSS v26 (IBM®). All data was then reported into a database and herein presented as results.

RESULTS

Two hundred-sixty-two records* were identified and screened from the title and abstract according to the inclusion criteria. No duplicates were detected. Thirty-one records were considered eligible and screened with a full-text evaluation. Twenty-two records were excluded with reasons, of which: five were excluded due to unspecified diagnosis, fifteen due to lack of outcomes, one for language, one for lack of full text. Nine studies were then selected for qualitative and quantitative analysis (Figure 1).

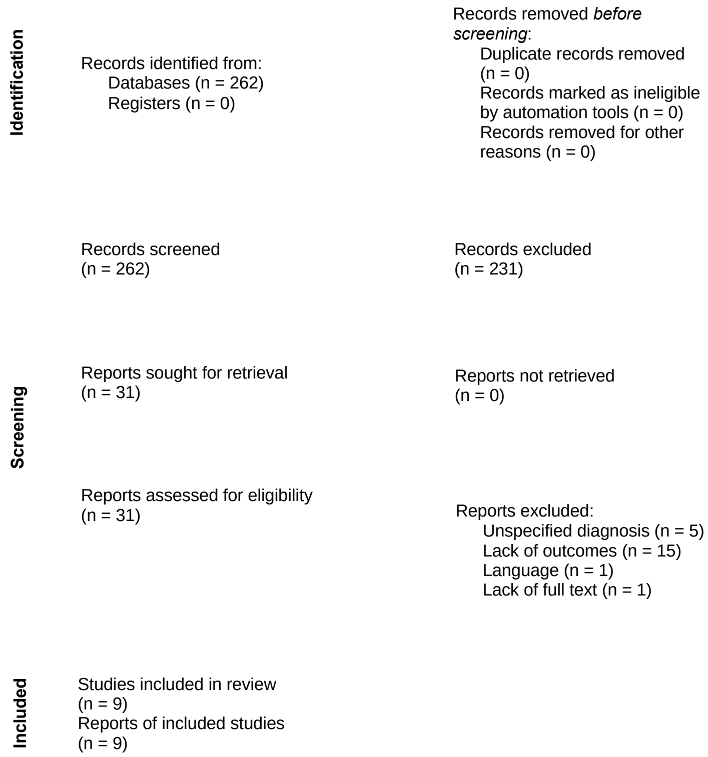

Figure 1. Study flow diagram. The number of records screened is accidentally the same as number of RLRs.

From our research, the total number of patients who underwent an RLR for CRCLM was 262, consisting of 161 males (61.5%), 97 females (37.0%) and 4 indeterminate (1.5%). The central value for the age varied between 59.0 and 72.0 years old in all the studies. The BMI varies from 23.4 to 28.0 between the studies.

The ASA score was expressed only in four studies: the percentage of ASA grade III-IV was 35.7% (n=10) in Ceccarelli et al., 81.7% (n=94) in Beard et al., 25.0% (n=3) in Navarro et al. and 83.3% (n=5) in Patriti et al [24-26]. None of the baseline characteristics constituted a contraindication to RLR.

The baseline characteristics of patients are listed in table 1.

Table 1. Baseline characteristics.

Study	Year	Study type	Type of Da Vinci Robot	Tot. N of cases	N of patients operated for CRCLM, N (%)	Age, years	Gender, M/F	BMI	ASA score, I-II/III-IV
Ceccarelli [24]	2021	Retrospective cohort	Si, Xi (since 2017)	28	28 (100)	Mdn 65.0 (IQR 5-73)	18/10	Mdn 27.5 (IQR 24-29)	18/10
Rahimli [27]	2020	Retrospective cohort	Si, Xi (since 2019)	25	12 (48)	M 63.5 (SD ±11.3)	6/6	M 26.2 (SD ±2.7)	N/A

Guadagni [28]	2020	Retrospective cohort	Si, Xi (since 2015)	20	20 (100)	M 66.1 (SD ±11.8)	13/7	M 24.4 (SD ±2.7)	N/A
Beard [25]	2019	Retrospective cohort	Si	629	115 (18.3)	M 61.0 (SD ±11)	76/39	M 28.0 (SD ±6)	21/94
Navarro [29]	2019	Retrospective cohort	Si, Xi	12	12 (100)	M 59.0 (Ra 37-77)	7/5	M 24.9 (SD ±2.4)	9/3
Guerra [30]	2019	Retrospective cohort	Si	59	59 (100)	Mdn 64.0 (Ra 43-84)	37/22	Mdn 26.0 (Ra 17-38)	N/A
Dwyer [31]	2018	Retrospective cohort	Si	6*	4 (67)	M 59.3	2/4	M 23.4	N/A
Croner [32]	2015	Retrospective cohort	Si	9	4 (44.4)	M 61.5 (SD ±13.3)	N/A	N/A	N/A
Patriti [26]	2008	Retrospective cohort	Si	7	6 (85.7)	M 72.0 (SD ±12)	2/4	M 26.2 (SD ±4.6)	1/5

M: mean; Mdn: median; SD: standard deviation; Ra: minimum-maximum; IQR: interquartile range; CRCLM: colorectal cancer liver metastases. *Two patients did not receive any liver resection (one ablation and one undetectable lesion at the ultrasound) but they were included in baseline data.

Only the paper by Ceccarelli et al. [24] is detailed enough to relate BMI, Age, ASA with complications. Authors reported complications Clavien-Dindo score >2 in 4 patients.

Baseline characteristics of the patients were: 2 (7.14%) patients ASA I/II, with mean age of 35(SD±5.6) and a BMI of 20.3 (SD±1); 2 (7.14%) patients were ASA III/IV with mean age of 64.5(SD±2.1) and a BMI of 28.12 (SD±4.1).

According to Brisbane classification, hepatic resections were classified as major if more of three segments were ablated [33]. Thirty-eight major resections were performed (14.5% of patients), in 15 cases simultaneously to primary cancer resection. One hundred and thirty-one procedures (50%) were performed simultaneously with resection of the primary tumor. In table 2 we reported are depicted in detail colorectal procedures associated to RLRs.

Operative data are shown in tables 3 and 4.

Table 2. Colorectal procedures associated to RLRs..

Study	Simultaneous resections, N (%)	Simultaneous colon resections (N, type of resections)	Simultaneous rectal resections (N, type of resections)
Ceccarelli [24]	28 (100)	16 (9 RH, 7LH)	12 (10 RAR, 1 HP, 1 MP)
Rahimli [27]	0 (0)	0	0

Guadagni [28]	3 (15)	2 (RH)	1 (1 MP)
Beard [25]	72 (62.6)	N/A	N/A
Navarro [29]	12 (100)	3 (2 RH, 1 LH)	9 (7 LRAR, 2 RAR)
Guerra [30]	4 (6.8)	4 (3 RH, 1 LH)	0
Dwyer [31]	6* (100)	1 (1 RH)	5 (3 LRAR, 2 RAR)
Croner [32]	0 (0)	0	0
Patriti [26]	6 (85.7)	5 (4 LH°, 1 RH°)	1 (1 TME°)

*Two patients did not receive any liver resection (one ablation and one undetectable lesion at the ultra-sound) but they were included in baseline data. RH: Right Hemicolectomy; LH: Left Hemicolectomy; RAR: Rectal Anterior Resection; HP: Hartmann Procedure; MP: Miles Procedure; LRAR: Low Rectal Anterior Resection; TME: Total Mesorectal Excision; °: laparoscopic.

Table 3. Operative characteristics 1.

Study	N of patients operated for CRCLM, N (%)	Pringle maneuver	Blood loss, ml	Operative times, minutes	Length of hospital stay, days
Ceccarelli [24]	28 (100)	Yes	Mdn 350 (IQR 200-500)	Mdn 332 (IQR 280-335)	Mdn 8 (IQR 7-13)
Rahimli [27]	12 (48)	No	M 450 (SD 278)	M 342 (SD 101.4)	M 9.3 (SD 4.2)
Guadagni [28]	20 (100)	N/A	M 250 (Ra 200-300)	M 198.5 (SD 98.0)	M 4.7 (SD 1.8)
Beard [25]	115 (18.3)	Yes	N/A	M 272 (SD 115)	Mdn 5 (IQR 3-6)
Navarro [29]	12 (100)	No	M 274.3 (Ra 40-780)	M 449 (Ra 135-682)	M 12 (Ra 5-28)
Guerra [30]	59 (100)	Yes	Mdn 200 (Ra 0-1500)	Mdn 210 (Ra 50-600)	M 6.7 (SD 6.2)
Dwyer [31]	4 (67)	N/A	M 316 (Ra 150-1000)	M 401 (Ra 349- 506)	Mdn 4.5 (Ra 3-10)
Croner [32]	4 (44.4)	Yes	N/A	M 321.2 (SD 67.9)	M 6.7 (SD 2.2)
Patriti [26]	6 (85.7)	Yes	M 256.7 (SD 193.2)	M 360 (SD 131.4)	M 8.5 (SD 1.2)

M: mean; Mdn: median; SD: standard deviation; Ra: minimum-maximum; IQR: interquartile range; CRCLM: colorectal cancer liver metastases

Table 4. Operative characteristics 2.

Study	N of patients operated for CRCLM, N (%)	Major resections, N (%)	Simultaneous resections, N (%)	Supero-posterior segments, N (%)	Conversion, N (%)
Ceccarelli [24]	28 (100)	2 (7.1)	28 (100)	18 (34.6)	2 (7.1)
Rahimli [27]	12 (48)	5 (41.7)	0 (0)	N/A	N/A
Guadagni [28]	20 (100)	0 (0)	3 (15)	N/A	0 (0)
Beard [25]	115 (18.3)	18 (15.6)	72 (62.6)	22 (19.1)	6 (5.2)
Navarro [29]	12 (100)	4 (33.3)	12 (100)	7 (58.3)	0 (0)
Guerra [30]	59 (100)	4/78 (5.1)*	4 (6.8)	N/A	7 (11.8)
Dwyer [31]	4 (67)	0 (0)	6 (100)	N/A	0 (0%)
Croner [32]	4 (44.4)	0 (0)	0 (0)	N/A	N/A
Patriti [26]	6 (85.7)	5 (83.3)	6 (85.7)	4 (57.1)	N/A

M: mean; Mdn: median; SD: standard deviation; Ra: minimum-maximum; IQR: interquartile range; CRCLM: colorectal cancer liver metastases. * Major/minor resections calculated on the total liver resections performed.

The central values for blood loss varied from 200 ml to 450 ml, operative times from 198.5 to 449.0 minutes and length of hospital stay from 4.5 to 12 days. Among the studies that reported the use of the Pringle maneuver, only Rahimli and Navarro affirmed that they did not perform the Pringle maneuver at all [27,29].

The overall postoperative mortality rate was 0.4%, as only one patient died for cardiac arrest in the Beard et al series [25]. The overall morbidity rate was 37.0% (n=97) and the major complication Clavien-Dindo grade III-IV rate was 8.4% (n=22). Resections with positive margins (R1/2) were found in 29 patients (11.1%). The Beard et al. series had the highest positive resection margin rate of 21.5%, followed by Guerra et al. and Ceccarelli et al. that reported rates of 8.5% and 3.6%, respectively [24,25,30].

Four series reported the OS outcomes: the 1-year OS rate was 90.4-100%, the 3-year OS was 44.4-66.1% and the 5-year OS was 37.0-61.0% [24,25,27,30].

Five series reported the DFS outcomes: the 1-year DFS was 44.4-89.5%, the 3-year DFS was 33.3-41.9% and the 5-year DFS was 38.0% [25,27,28,30,31].

Post-operative data are summarized in table 5.

Major colorectal and liver related complications are summarized in table 6 when available.

Table 5. Postoperative and follow-up outcomes.

Study	N of patients operated for CRCLM, N (%)	Mortality, N (%)	Minor complications (CD I-II), N (%)	Major complications (CD III-IV), N (%)	R1/2 Resections, N (%)	Overall survival	Disease-free survival, % (year)
Ceccarelli [24]	28 (100)	0 (0)	24 (85.7)	4 (14.3)	1 (3.6)	37-58% (5y)**	N/A
Rahimli [27]	12 (48)	0 (0)	2 (16.7)	1 (8.3)	0 (0)	100% (1y) 44.4% (3y)	44.4% (1y) 33.3% (3y)
Guadagni [28]	20 (100)	0 (0)	5 (25)	0 (0)	0 (0)	N/A	89.5% (1y) 35.8% (3y)
Beard [25]	115 (18.3)	1 (0.8)	24 (20.9)	12 (10.4)	23 (21.5)*	61.0% (5y)	38.0% (5y)
Navarro [29]	12 (100)	0 (0)	3 (25)	2 (16.6)	0 (0)	N/A	N/A
Guerra [30]	59 (100)	0 (0)	13 (22)	3 (5.1)	5 (8.5)	90.4% (1y), 66.1% (3y)	83.5% (1y) 41.9 % (3y)
Dwyer [31]	4 (67)	0 (0)	3 (50)	N/A	N/A	N/A	M 9.5 months
Croner [32]	4 (44.4)	0 (0)	1 (25)	0 (0)	0 (0)	N/A	N/A
Patriti [26]	6 (85.7)	0 (0)	0 (0)	0 (0)	N/A	N/A	N/A

CRCLM: colorectal cancer liver metastases; CD: Clavien-Dindo grade.* Up to 107 patients with identifiable tumour. **Among patients with R0 resections.

Table 6. Major colorectal and liver related complications

STUDY	Ceccarelli 24	Rahimli 27	Guadagni 28	Beard 25	Navarro 29	Guerra 30	Dwyer 31	Croner 32	Patriti 26
Tot. N of pts	28	12	20	115	12	59	6	4	6
Simultaneous robotic resections, n(%)	28 (100)	0 (0)	3 (15)	72 (62.6)	12 (100)	4 (6.8)	6* (100)	0 (0)	6 (100)
Steged approach, n(%)	0	12 (100)	17 (85)	43 (37.4)	0 (0)	52 (88.13)	0 (0)	4 (100)	0 (0)
Complications, n(%):									
anastomotic leakage	1 (3.57)	0	0	0	1 (8.3)	0	2 (33.3)	1(25)	0
Ileus	0	0	0	4 (3.5)	0	0	0	0	0
surgical infection	0	0	0	0	1 (8.3)	0	0	0	0
perineal wound healing	0	0	0	0	0	0	1 (16.7)	0	0
pelvic abscess	0	0	0	0	0	0	2 (33.3)	0	0
enterocutaneous fistula	0	1 (8.33)	0	0	0	0	0	0	0
Lymphocele	0	1 (8.33)	0	0	0	0	0	0	0
biliary leak	0	1 (8.33)	0	0	0	1 (1.7)	0	0	0
intra-abdominal abscess	0	0	0	7 (6.1)	2 (16.7)	0	0	0	0
Ascites	0	0	0	0	1 (8.3)	0	0	0	0

* Two patients did not receive any liver resection (one ablation and one undetectable lesion at the ultrasound).

DISCUSSION

As stated by the international Southampton guidelines, the minimally invasive approach to liver metastases allows a parenchymal sparing liver surgery and improves the short-term outcomes compared with the open approach, without affecting the long-term outcomes [6]. It has been demonstrated that intraoperative and postoperative short and long-term outcomes such as blood loss, length of hospital stay, R0 resection rate, OS and DFS were comparable between the minimally invasive and open groups [2-4,14].

It has been proven that when primary colorectal cancer and liver metastases are both eligible for surgery at the same time, simultaneous resections can be performed with good oncological results [34-37].

However, when are required major liver resections or complex colorectal procedures, a delayed approach may provide better perioperative outcomes [7,38,39].

Robotic surgery was introduced at the beginning of the century to overcome the limits of laparoscopy, especially in complex and simultaneous resections, offering articulated arms and a high-definition three-dimensional view [40-45].

Despite the wide spread of robotic surgery, the experience on robotic resection of CRCLMs is still very poor in the literature, limited only to small case-series in retrospective studies. Therefore, our systematic review provides a clear overview of the currently available data on RLRs for CRCLM on a total of 262 patients among 9 studies.

In order to better understand the impact of our review in the HPB context we compared our results to other laparoscopic and open series reported in literature [46-49].

Base-line characteristics and BMI

In our review we analyzed 262 patients with mean age of 63.2 yrs, the 63.6% (161/253) were male [9,24,25,27-32].

Baseline characteristics of patients are superimposable to other experiences on liver surgery reported in literature. We compared our data to the cases series published by Kasai, Fretland and Robles-Campos were 264 patients underwent OLR were put in relationship with 249 underwent LLR with a mean age of 67.3 yrs and 66 yrs respectively. The male/female ratio was 3:2 in the open group and 7:10 in the Laparoscopic group[50-52].

Furthermore, concerning mean age , a recent review published in 2021 by McGuirk et al. analyzed 28 patients underwent RLRs for simultaneous CRLMs and it shows a similar data (62.5 yrs)[19].

Regarding obese patients a high BMI is often associated with metabolic, hepatic and cardiopulmonary comorbidities, however, we report in the selected studies a mean BMI often major than 25. As already depicted in literature by Viganò, obesity should not dissuade surgeons from using a robotic approach to liver resections[53]. The robotic technique appears to be safe and feasible in also patients with high BMI[53].

Concerning ASA score, only four of nine studies collected in the review reported the data [9,24,25,29], for this reason it is not possible to extensively discuss the topic, but we would underline that the multicentric study by Beard et al. on 115 patients, reported 94 (81.74%) patients with ASA≥3 [25]. Despite ASA score does not seem to be a contraindication to robotic surgery, more wide studies are needed to investigate the topic.

Operative Time

It is well known that one of the drawbacks of robotic surgery is longer operating time, as already highlighted in literature [54]. The operating times found in our research are quite heterogeneous, with a range of central values of 250.5 minutes. If we analyze different papers included in our review, we found that Rahimli comparing RLR to LRL found a significantly longer operating time in the robotic approach (mean 342 min *vs.* 200 min), on the other hand the larger series by Beard et al. did not report statistically different operating times between the two groups (RLR mean 272 min *vs.* LRL 253 min, p=0.12) [25,27].

Although, the mean operative time reported in the recent review by McGuirk was 420.3 min, 68% longer than the average operating time found in our review, on the hand Navarro and Dwyer series reported superimposable operating time [19,29,31].

We compared robotic data with other laparoscopic and open CRLMs resections. LLRs by Kasai 2017, Fretland 2018 and Robles-Campos 2019 showed a mean operative time of 268′, 123′, 120′ respectively for LLR and a mean operative time of 301′, 120′, 131.66′ for OLR [50-52]. It appears quite clear that laparoscopic approach is more widely diffused with a technique standardization which allows faster operating times, but to the date it is not possible to clearly define the limits and the perspectives of RLRs related to operating time, because the lack of experience due to the small number of patients treated in a wide range of time.

However the latest generation of the Da Vinci Xi® allows a faster docking and it needs less skills to be managed, so future reports might change the present scenario [55].

We shall investigate only CRLMs resections because if we compared data to other indications to liver surgery, like HCC, we found in literature that the robotic approach requires longer operative time probably as consequence of the underlining liver injury and the less incidence of parenchymal sparing indications [56-62].

After the introducing of Da Vinci System at beginning of the last century, Ho et. al in 2012 reported a systematic review of 217 patients underwent RLRs for benign and malignant liver disease (HCC, Cholangiocarcinoma, metastases). The mean operative time reported at that time was longer than the average reported in the present review, but it should be considered that we analyzed data after 10 years of technological development in MIS and we selected only CRCLM. (313.83 min *vs.* 250.5 min) [21].

Blood loss

Robotic approach seems to be safe and effective in terms of blood loss compared to open and laparoscopic surgery [2,10,15,21,40,53]. In our review we found a mean blood loss of 309.4 ml vs. 150 ml reported in the Laparoscopic serie by Kasai, 300 ml reported in the Laparoscopic serie by Fretland, 150 ml reported in the Laparoscopic Robles-Campos and 365 ml reported in the Laparoscopic Croner serie [50-52,63].

Moreover, the estimated blood loss reported in our 9 case-series is superimposable to the available and recent paper in literature[19].

Also comparing the different approaches during HCC resection, current data available in literature shows a similar trend in terms of blood loss [24-32,50-52,56,59,63].

However, it should be noted that the management of intraoperative bleeding can vary between different centers despite the type of surgical approach. For example, the Pringle maneuver, which might be very useful to manage liver bleeding during transection was used only in Ceccarelli, Beard, Guerra, Croner and Patriti series, but we underline that the majority of authors claimed to prepare the hepatic pedicle before transection [24-26,30,32]. Unfortunately, studies included in the review does not allow a proper analysis on transfusion policy, because transfusion rate are often not declared [24,31,32] . However, it is conceivable that robotic procedures allow an effective management of intraoperative bleeding also thanks to endo-wrist technology and 3D vision.

In the previous decade, Ho et al. reported a mean blood loss of 485.16 ml (range of average: 50-660 ml) that was the 57% more than our value (309.4 ml), the technological development and the improvement of the learning curve may explain these results [21].

Complications

As already extensively discussed by Haney et al. in a recent review on laparoscopic vs open liver resections, the minimally invasive approach seemed to be safer for minor liver resections when performed in minimally invasive surgery [46].

Rahimli et al. is the only author who clearly reported differences in peri-operative outcomes comparing minor to major RLRs [27]. Minor resections were statistically faster, requiring less hospital stay and showing less blood loss. The other peri-operative outcomes, including R0 resection rate, did not differ between the two groups.

The overall major complication rate classified as Clavien Dindo ≥3 in our robotic review is 20/258 (7,75%) patients. Compared to other laparoscopic and open series we found that Kasai, Fretland and Robles-Campos reported 22 (8.98%) Clavien Dindo ≥3 complications on 245 LLR and 36 (13.80%) Clavien Dindo ≥3 complications on 261 OLR (Table 6) [9,24,25,27-32,50-52].

Cipriani et al. in a huge series of 367 CRLMs resections reported 26/133 (19.55%) Clavien-Dindo ≥3 complications in the open series and 18/133 (13.50%) Clavien-Dindo ≥3 complicated patients in the laparoscopic one [49].

The conversion rate reported during robotic resections retrieved in the present review is 5.7%. This data is superimposable to laparoscopic convention rate showed by Quijano, Wu, Troisi and Cipriani either for CRLMs either for HCC resections [24-32,49,58,59,61,64,65].

Beard et al. also declared that despite robotic procedures were more challenging, however the conversion rate was higher for the laparoscopic group.

If we analyze the margin status, we found a very high R1 rate of 21% in the Beard experience, similar for both cohort of patients LLR and RLR [25]. This finding is in antithesis to the results recently achieved by several authors, who reported an R0 resection rate higher than 90% for different type of RLR including HCC and CRLMs [40,43,63,66-70].

Excluding Beard et al., 8 of the 9 authors cited in this review respect the R0 standard of care achieving a cancer free margin specimens in more than 90% of cases [9,24,27-32]. About the experience of Beard et al. the authors explained in their discussion the reasons of the high R1 resection rate affirming that the 15 years period of collections of cases might be the cause of the positive margin status as consequence of the learning curve in minimally invasive liver surgery [25].

Hospital Stay

Also concerning hospital stay, we compared our data with other reports on open and laparoscopic liver surgery published in literature. The laparoscopic resections for CRLMs showed a mean hospital stay of 4.5 days [50-52].

Indeed, the open liver surgery for CRLM demonstrates a hospital stay of 6.87 days as mean, while the robotic approach showed a longer hospital stay of 7.98 days as mean [24-32,49-52,56]. McGuirk review reports superimposable data (8.6 days *vs*. 7.98 days)[19].

It is difficult to explain the reason why the robotic approach needed a longer hospital stay, but probably the low experience in robotic resections in several centers not dedicated to HPB caused a delayed recovery.

Regarding HCC also other authors reported superimposable recovery data (mean hospital stay 6.11 days, 7.4 days and 8 days for laparoscopic, open and robotic approach) [56,58-60].

From this point of view in the last ten years it is not possible to find a real improvement, so we can underline how Ho et al. in 2012 reported as hospital stay in patients underwent RLRs for benign and malignant disease 7.93 days *vs.* 7.98 [21].

Simultaneous resections and correlated complications

The systematic review by Garritano et al. reported the results of 20 series of simultaneous operations achieved in MIS, both laparoscopic and robotic, concluding that the one-stage approach allows a faster discharge and faster access to chemotherapy than the delayed approach [17]

From our review we found 131 patients treated for synchronous metastasis with simultaneous resections.

In the multicentric study by Beard et al. we found 72 patients underwent simultaneous resection, but the paper does not clearly report peri-operative data, so we could not perform further analysis on them. On the other hand, authors declared that the majority of patients underwent robotic resection were more complex cases and often patients underwent simultaneous procedures [25]. So we analyzed data from the remaining 57 simultaneous liver resections (two patients reported by Dwyer were treated with non-surgical techniques) to better investigate the impact of synchronous surgery on peri-operative outcomes: a total of 11 (19.30%) adverse events are reported, more in detail we found 4 (7%) anastomotic leakage, 2 (3.5%) abscess, 2 (3.5%) intra-abdominal abscess, 1 (1.75%) perineal wound healing, 1 (1.75%) surgical infection, 1 (1.75%) ascites [24,26,29,31].

OS and DFS

OS and DFS are the main goal of CRLM resections. Despite this consideration only few papers clearly reported long term outcomes. It was possible to determine the 3 yrs OS only for 71 of 262 patients included in the review, showing a 3 yrs. OS of 55.25% and a 37% DFS available for 91of 262 patients [27,28,30].

Regarding laparoscopic experiences, a literature review including 382 patients underwent CRLM surgery showed a 76% 3 years OS and 35% DFS [49-52].

On the other hand, 397 patients underwent open surgery for CRLMs, showed a 65% OS-3years and DFS is 37% [49-52]. There are not enough data to explain why robotic approach showed a less OS and similar DFS if compared to other approaches, in our opinion there too many biases like selection of patients, biology of the tumor, cause of death, to allow further hypothesis.

Volume and centres

Despite current trends reported in literature clearly suggest to perform liver surgery in high volume referral centers, in our review we observed that the majority of robotic CRLMs resections were performed in general surgery units [71]. Moreover, it was not possible to demonstrate a clear correlation between case volume and complication rates.

Comparing our data with data reported by referral centers for HPB surgery with a huge experience in laparoscopic liver surgery, so we can underline that through the robot assisted approach, general surgeons even if they are not dedicated to HPB may achieve peri-operative outcomes superimposable to the standard of care [24,26,27,29].

Costs

None of the included studies reported cost data. One of the most popular drawbacks of robotic surgery is its cost-effectiveness, which is apparently more disadvantageous than conventional techniques.

As already published by Ceccarelli et. al. the robotic platform may allow general surgeons to perform minimally invasive liver surgery with the advisable objective of health mobility reduction to HPB referral centers. Health mobility should be investigated in further studies which have the goal to analyze the cost/benefits of robotic technology [72]. Croner et al. calculated the perioperative costs of surgical procedures, as result he declared that to the date the robotic procedures cost 228% more than open ones and 155% more than laparoscopic surgery [63].

Limitations

The limitations of this systematic review are due to the included studies, which consist of small series of retrospective cases. Unfortunately, some data are not available or not clearly declared in the papers, so we can only discuss what authors reported about their experiences. Despite our effort to the date, data are still too heterogeneous and almost all papers are retrospective, therefore it is very difficult to obtain strong conclusions from the study.

CONCLUSIONS

Despite robotic liver surgery has gained great diffusion in the last twenty years, the robotic-assisted approach to CRCLM has never been investigated in large series.

At the beginning Robotic liver resection were considered safe and feasible if performed in experienced hands, but long-term oncologic outcomes were very unclear and short-term outcomes indicated RLRs similar to laparoscopy [21].

Nowadays, this systematic review shows that robotic-assisted surgery might be considered as a technical upgrade option for MI approach to CRCLM resections even for simultaneous operations and challenging cases.

To date, there are no prospective randomized studies comparing robotic re-sections of CRCLMs with laparoscopic and open techniques, so assessments can only be made on small series of retrospective cases. Further studies will better clarify the advantages and disadvantages of robotic surgery for the resection of CRCLMs.

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Table 1. Baseline characteristics.

Study	Year	Study type	Type of Da Vinci Robot	Tot. N of cases	N of patients operated for CRCLM, N (%)	Age, years	Gender, M/F	BMI	ASA score, I-II/III-IV
Ceccarelli [24]	2021	Retrospective cohort	Si, Xi (since 2017)	28	28 (100)	Mdn 65.0 (IQR 5-73)	18/10	Mdn 27.5 (IQR 24-29)	18/10
Rahimli [27]	2020	Retrospective cohort	Si, Xi (since 2019)	25	12 (48)	M 63.5 (SD ±11.3)	6/6	M 26.2 (SD ±2.7)	N/A
Guadagni [28]	2020	Retrospective cohort	Si, Xi (since 2015)	20	20 (100)	M 66.1 (SD ±11.8)	13/7	M 24.4 (SD ±2.7)	N/A
Beard [25]	2019	Retrospective cohort	Si	629	115 (18.3)	M 61.0 (SD ±11)	76/39	M 28.0 (SD ±6)	21/94
Navarro [29]	2019	Retrospective cohort	Si, Xi	12	12 (100)	M 59.0 (Ra 37-77)	7/5	M 24.9 (SD ±2.4)	9/3
Guerra [30]	2019	Retrospective cohort	Si	59	59 (100)	Mdn 64.0 (Ra 43-84)	37/22	Mdn 26.0 (Ra 17-38)	N/A
Dwyer [31]	2018	Retrospective cohort	Si	6*	4 (67)	M 59.3	2/4	M 23.4	N/A
Croner [32]	2015	Retrospective cohort	Si	9	4 (44.4)	M 61.5 (SD ±13.3)	N/A	N/A	N/A
Patriti [26]	2008	Retrospective cohort	Si	7	6 (85.7)	M 72.0 (SD ±12)	2/4	M 26.2 (SD ±4.6)	1/5

M: mean; Mdn: median; SD: standard deviation; Ra: minimum-maximum; IQR: interquartile range; CRCLM: colorectal cancer liver metastases. *Two patients did not receive any liver resection (one ablation and one undetectable lesion at the ultrasound) but they were included in baseline data.

Table 2. Colorectal procedures associated to RLRs..

Study	Simultaneous resections, N (%)	Simultaneous colon resections (N, type of resections)	Simultaneous rectal resections (N, type of resections)
Ceccarelli [18]	28 (100)	16 (9 RH, 7LH)	12 (10 RAR, 1 HP, 1 MP)
Rahimli [19]	0 (0)	0	0
Guadagni [20]	3 (15)	2 (RH)	1 (1 MP)
Beard [21]	72 (62.6)	N/A	N/A
Navarro [22]	12 (100)	3 (2 RH, 1 LH)	9 (7 LRAR, 2 RAR)
Guerra [23]	4 (6.8)	4 (3 RH, 1 LH)	0
Dwyer [24]	6* (100)	1 (1 RH)	5 (3 LRAR, 2 RAR)
Croner [25]	0 (0)	0	0
Patriti [26]	6 (85.7)	5 (4 LH°, 1 RH°)	1 (1 TME°)

*Two patients did not receive any liver resection (one ablation and one undetectable lesion at the ultra-sound) but they were included in baseline data. RH: Right Hemicolectomy; LH: Left Hemicolectomy; RAR: Rectal Anterior Resection; HP: Hartmann Procedure; MP: Miles Procedure; LRAR: Low Rectal Anterior Resection; TME: Total Mesorectal Excision; °: laparoscopic.

Table 3. Operative characteristics 1.

Study	N of patients operated for CRCLM, N (%)	Pringle maneuver	Blood loss, ml	Operative times, minutes	Length of hospital stay, days
Ceccarelli [18]	28 (100)	Yes	Mdn 350 (IQR 200-500)	Mdn 332 (IQR 280-335)	Mdn 8 (IQR 7-13)
Rahimli [19]	12 (48)	No	M 450 (SD 278)	M 342 (SD 101.4)	M 9.3 (SD 4.2)
Guadagni [20]	20 (100)	N/A	M 250 (Ra 200-300)	M 198.5 (SD 98.0)	M 4.7 (SD 1.8)
Beard [21]	115 (18.3)	Yes	N/A	M 272 (SD 115)	Mdn 5 (IQR 3-6)
Navarro [22]	12 (100)	No	M 274.3 (Ra 40-780)	M 449 (Ra 135-682)	M 12 (Ra 5-28)
Guerra [23]	59 (100)	Yes	Mdn 200 (Ra 0-1500)	Mdn 210 (Ra 50-600)	M 6.7 (SD 6.2)
Dwyer [24]	4 (67)	N/A	M 316 (Ra 150-1000)	M 401 (Ra 349- 506)	Mdn 4.5 (Ra 3-10)
Croner [25]	4 (44.4)	Yes	N/A	M 321.2 (SD 67.9)	M 6.7 (SD 2.2)
Patriti [26]	6 (85.7)	Yes	M 256.7 (SD 193.2)	M 360 (SD 131.4)	M 8.5 (SD 1.2)

M: mean; Mdn: median; SD: standard deviation; Ra: minimum-maximum; IQR: interquartile range; CRCLM: colorectal cancer liver metastases

Table 4. Operative characteristics 2.

Study	N of patients operated for CRCLM, N (%)	Major resections, N (%)	Simultaneous resections, N (%)	Supero-posterior segments, N (%)	Conversion, N (%)
Ceccarelli [18]	28 (100)	2 (7.1)	28 (100)	18 (34.6)	2 (7.1)
Rahimli [19]	12 (48)	5 (41.7)	0 (0)	N/A	N/A
Guadagni [20]	20 (100)	0 (0)	3 (15)	N/A	0 (0)
Beard [21]	115 (18.3)	18 (15.6)	72 (62.6)	22 (19.1)	6 (5.2)
Navarro [22]	12 (100)	4 (33.3)	12 (100)	7 (58.3)	0 (0)
Guerra [23]	59 (100)	4/78 (5.1)*	4 (6.8)	N/A	7 (11.8)
Dwyer [24]	4 (67)	0 (0)	6 (100)	N/A	0 (0%)
Croner [25]	4 (44.4)	0 (0)	0 (0)	N/A	N/A
Patriti [26]	6 (85.7)	5 (83.3)	6 (85.7)	4 (57.1)	N/A

M: mean; Mdn: median; SD: standard deviation; Ra: minimum-maximum; IQR: interquartile range; CRCLM: colorectal cancer liver metastases. * Major/minor resections calculated on the total liver resections performed.

Table 5. Postoperative and follow-up outcomes.

Study	N of patients operated for CRCLM, N (%)	Mortality, N (%)	Minor complications (CD I-II), N (%)	Major complications (CD III-IV), N (%)	R1/2 Resections, N (%)	Overall survival	Disease-free survival, % (year)
Ceccarelli [18]	28 (100)	0 (0)	24 (85.7)	4 (14.3)	1 (3.6)	37-58% (5y)**	N/A
Rahimli [19]	12 (48)	0 (0)	2 (16.7)	1 (8.3)	0 (0)	100% (1y) 44.4% (3y)	44.4% (1y) 33.3% (3y)
Guadagni [20]	20 (100)	0 (0)	5 (25)	0 (0)	0 (0)	N/A	89.5% (1y) 35.8% (3y)
Beard [21]	115 (18.3)	1 (0.8)	24 (20.9)	12 (10.4)	23 (21.5)*	61.0% (5y)	38.0% (5y)
Navarro [22]	12 (100)	0 (0)	3 (25)	2 (16.6)	0 (0)	N/A	N/A
Guerra [23]	59 (100)	0 (0)	13 (22)	3 (5.1)	5 (8.5)	90.4% (1y), 66.1% (3y)	83.5% (1y) 41.9 % (3y)
Dwyer [24]	4 (67)	0 (0)	3 (50)	N/A	N/A	N/A	M 9.5 months
Croner [25]	4 (44.4)	0 (0)	1 (25)	0 (0)	0 (0)	N/A	N/A
Patriti [26]	6 (85.7)	0 (0)	0 (0)	0 (0)	N/A	N/A	N/A

CRCLM: colorectal cancer liver metastases; CD: Clavien-Dindo grade.* Up to 107 patients with identifiable tumour. **Among patients with R0 resections.

Table 6. Major colorectal and liver related complications

* Two patients did not receive any liver resection (one ablation and one undetectable lesion at the ultrasound).

STUDY	**Ceccarelli** [24]	**Rahimli** [27]	**Guadagni** [28]	**Beard** [25]	**Navarro** [29]	**Guerra** [30]	**Dwyer** [31]	**Croner** [32]	**Patriti** [26]
Tot. N of pts	28	12	20	115	12	59	6	4	6
Simultaneous robotic resections, n(%)	28 (100)	0 (0)	3 (15)	72 (62.6)	12 (100)	4 (6.8)	6* (100)	0 (0)	6 (100)
Steged approach, n(%)	0	12 (100)	17 (85)	43 (37.4)	0 (0)	52 (88.13)	0 (0)	4 (100)	0 (0)
Complications, n(%):									
anastomotic leakage	1 (3.57)	0	0	0	1 (8.3)	0	2 (33.3)	1(25)	0
Ileus	0	0	0	4 (3.5)	0	0	0	0	0
surgical infection	0	0	0	0	1 (8.3)	0	0	0	0
perineal wound healing	0	0	0	0	0	0	1 (16.7)	0	0
pelvic abscess	0	0	0	0	0	0	2 (33.3)	0	0
enterocutaneous fistula	0	1 (8.33)	0	0	0	0	0	0	0
Lymphocele	0	1 (8.33)	0	0	0	0	0	0	0
biliary leak	0	1 (8.33)	0	0	0	1 (1.7)	0	0	0
intra-abdominal abscess	0	0	0	7 (6.1)	2 (16.7)	0	0	0	0
Ascites	0	0	0	0	1 (8.3)	0	0	0	0

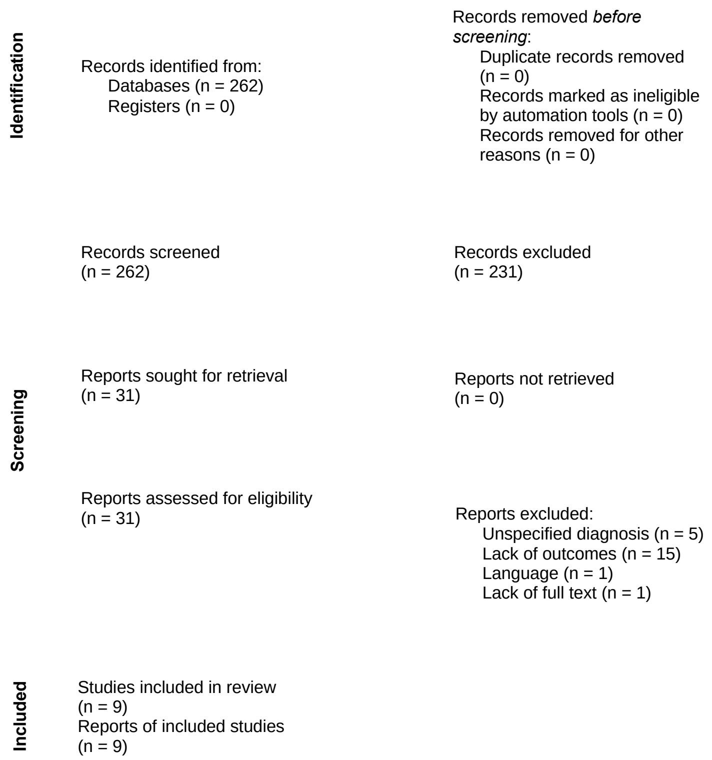

Figure 1. Study flow diagram. The number of records screened is accidentally the same as number of RLRs.