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Review

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Robotic *vs.* laparoscopic resection for hepatocellular carcinoma

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Abstract
Minimally invasive liver surgery (MILS) has become increasingly popular over the last two decades, with hepatocellular carcinoma (HCC) representing a common indication. While data has shown the benefits of a laparoscopic *vs.* an open approach, robotic liver surgery is rapidly emerging. In this context, among the two minimal access approaches [robotic (RLR) *vs.* laparoscopic liver resection (LLR)], a differential benefit is still under investigation. While the advantages of RLR include increased dexterity, reduction of physiological tremors, and wrist articulation, it currently has no haptic feedback or specialized liver parenchymal transection devices and is associated with increased operative time and cost. However, RLR has proved to be a safe and effective approach for select patients with HCC. Some benefits of RLR include similar oncological outcomes to open or laparoscopic surgery, possibly reduced conversion rates, and an easier transition from open surgery to a minimally invasive approach. Moreover, while already today RLR can facilitate resection for HCC in hard-to-reach anatomic locations (e.g., transthoracic approach to posterior-superior liver), the future of robotics with the development of advanced image processing technologies, haptic feedback, liver-specific devices, lower cost, and more robot choices seems even more promising.

Keywords: Hepatocellular carcinoma, minimally invasive liver surgery, robotic surgery, robotic liver surgery, robotic liver resection

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INTRODUCTION

Liver resection (LR) can be performed through an open (OLR), laparoscopic (LLR), or robotic approach (RLR). Advantages of minimally invasive liver surgery (MILS) include reduction of perioperative blood loss, postoperative pain, morbidity, and hospital stay[1,2]. In this context, hepatocellular carcinoma (HCC) is currently one of the most common indications for MILS, ranging from 26% to 40% of all the indications in large MILS series[1,3,4]. For patients with HCC, literature has suggested that LLR can be superior to OLR[2,5]. in selected circumstances, leading to advantageous short-term results in both cirrhotic and non-cirrhotic patients[6-8]. The benefits specific to robotic surgery help to overcome several limitations associated with a laparoscopic approach. The recognized benefits of using robotics include consistent three-dimensional (3D) visualization (which is also an option for LLR), increased dexterity and wrist articulation (facilitating suturing and vessel dissection), reduction of physiological tremors, increased accessibility to challenging parts of the liver such as the caudate lobe and right posterior liver segments, and a reduced learning curve[9-11]. Comparative clinical outcomes are still under study. Between 2010 to 2016, the use of RLR increased by fivefold in the U.S. and it is associated with a shorter hospital length of stay compared to the open approach without compromising perioperative outcomes or survival[12]. Additionally, it has been noted that oncologic outcomes have been comparable between LLR and RLR[10,13].

In this paper, we discuss RLR for patients with HCC by focusing on its benefits and drawbacks compared to a traditional laparoscopic approach.

METHODS

To find pertinent articles, three of the authors (E.P, A.M.C., and B.H) reviewed the literature and agreed to select the most relevant papers. In particular, the following keywords were used to conduct the research on PubMed, Google Scholar, and Scopus: "hepatocellular carcinoma" or "HCC" in association with "robotic hepatectomy", "robotic liver resection", or "robotic liver surgery".

GENERAL PRINCIPLES OF ROBOTIC LIVER RESECTION

Indications

The surgical indications for LR using a laparoscopic or robotic approach tend to overlap significantly[14]. A crucial indication to sway towards RLR instead of LLR would be in cases of tumors residing in the posterior and/or superior segments or in cases where a transthoracic approach is planned. The increased degrees of freedom associated with robotic surgery may allow for a more effective resection in these patient populations[15-17].

Patient selection based on liver function

Patient selection for HCC resection can be initially classified into two major categories depending on liver functional status: cirrhotic *vs.* non-cirrhotic. The former comes with increased operative mortality and rate of recurrence and a decreased hepatic regenerative capacity. This creates a difficult clinical balance between resecting enough parenchyma to ensure good surgical margins and minimizing the risk of local recurrence but also conserving functional tissue to prevent postoperative liver failure[11]. Patients with known liver disease can be stratified further by examining liver function, notably by using the Child-Pugh Score. Traditionally, only patients with Child-Pugh A class are considered surgical candidates due to poor liver function and post-surgical prognosis of Child-Pugh B and C patients. Nevertheless, LLR proved to be beneficial in select patients with HCC over Child-Pugh B cirrhosis[18,19]. Additionally, a high Model for End-Stage Liver Disease (MELD) score and the presence of cirrhosis have an independent negative effect on mortality after liver resection, and the MELD score is associated with postoperative morbidity among patients selected for hepatectomy[20]. In this setting, the fact that MILS is associated with a lower risk of postoperative ascites should be considered[21]. This may be due to the reduced disruption of parietal collateral blood flow associated with MILS.

Preoperative preparation

Today, advanced liver surgery planning can be achieved by using preoperative three-dimensional (3D) liver modeling to perform a virtual hepatectomy. 3D reconstruction utilizes specialized software with stereoscopic data that aids surgeons in identifying correct anatomical relationships and assessing the future remnant liver volume before going to the operating room. This is especially useful in MILS , as it enables modeling of the spatial relationship of anatomic structures, assessing for variant anatomy, and ensuring that surgery can proceed as safely as possible[17]. Additionally, the simulation of the port sites to align the eye-port-instrument-target-monitor axis will optimize ergonomics for the surgical team.

A recent systematic review by Jiang *et al.*[22] examined 16 studies that elucidated the differences between the usage of 3D vascular reconstruction and navigation technologies *vs.* a surgical approach without 3D modeling for primary hepatic carcinomas. Their study revealed statistically significant improved operation time and intraoperative blood loss in the group that had modeling.

Patient positioning and robotic set-up

When performing an RLR, patients are positioned supine, in the reverse Trendelenburg position at an angle of 20-35 degrees, and can be slightly tilted to the left, if needed[23,24]. Four to five trocars are used based on the procedure performed, with one serving as a camera port. Two to three ports are occupied by robotic arms, while the remaining ones are used for surgical assistance. The surgical trocars are placed according to the liver segment to be resected in the upper right and left quadrants[25-27]. The da Vinci® robotic surgical system patient cart is located at the patient's head, allowing for the robotic arms to be docked at the surgical site[23,27]. The surgeon sits at the surgeon console for the duration of the surgery, which has been reported to reduce physician fatigue. Further, the surgeon views the operative field in high-definition 3D images of the surgical site. The controls on the console have EndoWrist technology that provides seven degrees of motion. Both features can enhance precision and hand-eye coordination[28].

Intraoperative navigation

Utilizing the robot allows for the use of near-infrared fluorescence imaging with the fluorophore indocyanine green (ICG), which can help identify lymphatic structures, assess perfusion of parenchyma, and distinguish between healthy liver tissue *vs.* tumor tissue[17]. With this technology, surgeons can discern between the biliary tract and vasculature with greater detail, allowing for more precise dissection planes and resection margins while also minimizing the risk of intraoperative complications and remnant liver ischemia[29,30]. A panel of 13 experts in the Asia-Pacific region recommends fluorescence cholangiography to help identify extrahepatic biliary anatomy and recognize subcapsular tumors within 8 mm of the liver surface. This tool can also facilitate delineating segmental boundaries for MILS, while the concurrent use of IOUS is required in positive staining (Class IIb recommendation; Level II-2 evidence)[31].

For resection of deep HCC, the guidance of fluorescence imaging may reduce the risk of positive margins (Class IIa recommendation; Level II-3 evidence).

Augmented reality techniques can help not only in preoperative planning but also as intraoperative navigation tools. Today no robotic platform allows for augmented reality integration into the imaging platform. Volonté *et al.*[32] reported their experience with the OsiriX (Pixmeo, Geneva, Switzerland), an image processing software package dedicated to DICOM® images. In particular, OsiriX was helpful in allowing exact identification of the nodule position, helping in port placement and visual triangulation with laparoscopic instruments by projecting image overlays on the patient's abdomen. This allowed for an optimal docking of the robot, which is crucial. Also, it enabled the fusion of 3D reconstructed images and stereoscopic vision for RLR. Similarly, Bijlstra *et al.*[33] developed and validated the 3DeliverS Software. The software creates virtual reality 3D models based on imaging segmentation, which are integrated into a multimodal image-guided robotic liver surgery cockpit, guiding LR with an accuracy of 93%.

Our group utilizes the Synapse Vincent software (Fujifilm, Tokyo, Japan) for preoperative computed tomography (CT) based reconstruction[34]. It is our policy to always obtain a 3D reconstruction before MILS. In particular, we demonstrated how simulation is pivotal in the identification of hepatic veins tributaries and anatomic relationships between portal pedicles when performing major hepatectomies[35,36].

Learning curve

Regarding the learning curve for RLR, the standard practice involves preoperative mastery with simulation exercises to familiarize oneself with the robotic technology. It has been noted that 45 major hepatectomies, followed by 30 cases, are required to overcome the learning curve and have mastery of complex liver resections when performed laparoscopically[37]. When comparing the learning curve of a robot-assisted *vs.* laparoscopic surgery, there has been a reduced learning curve to mastery reported for RLR. Further, it was identified that 8-10 intermediate- and lower-level resections are required to be performed before difficult resections[26]. Nevertheless, a more recent report warrants caution, indicating an initial learning phase of 117 cases for LLR and 93 procedures for RLR, respectively[38]. An increase in blood transfusion, conversion, and operative time was noted during the learning phase, reaching a steady state subsequently after complexity-adjusted analysis.

ROBOTIC LIVER RESECTION FOR HEPATOCELLULAR CARCINOMA

One of the first case series reporting short-term outcomes after RLR for HCC[23] described the outcomes of 41 consecutive patients with HCC undergoing 42 resections, with 23.8% being major LR. The mean operating time and blood loss were 229.4 min and 412.6 mL, respectively. The R0 resection rate was 93%, and postoperative mortality and morbidity rates were 0% and 7.1%, respectively. The mean hospital stay was 6.2 days. The 2-year overall (OS) and disease-free survival (DFS) rates were 94% and 74%, respectively. The authors performed a subgroup analysis of minor (< 3 Couinaud segments) RLR *vs.* conventional minor LLR. They showed how the robotic group had similar blood loss (mean, 373.4 mL *vs.* 347.7 mL), morbidity (3% *vs.* 9%), mortality (0% *vs.* 0%), and R0 resection rate (90.9% *vs.* 90.9%). However, the robotic group had a significantly longer operative time (202.7 min *vs.* 133.4 min).

Further reports[13,39-50] confirmed similar outcomes in terms of operative time, surgical radicality, perioperative mortality and morbidity, and postoperative length of stay. More variability was noted in terms of major resection and conversion to laparotomy rates, and blood loss. However, all these early case series were small (the number of cases described ranged from 10 to 140) with different rates of cirrhotic patients (from 26.2% to 97.5%), as shown in Table 1.

Several authors have compared the outcomes of RLR for HCC to those after OLR. After propensity scored matching, Chen *et al.*[41] demonstrated in comparable groups [major liver resections (41.9 *vs.* 39.5 %) and liver cirrhosis (45.7 *vs.*46.9 %)] that while the robotic group required longer operation times (343 *vs.* 220 min), RLR led to shorter hospital stays (7.5 *vs.* 10.1 days) and improved postoperative pain. The 3-year DFS and OS of the robotic group were comparable with that of the open group (72.2% *vs.* 58.0%; $P = 0.062$ and 92.6% *vs.* 93.7%; $P = 0.431$).

Table 1. A summary of papers describing outcomes after robotic liver resection for hepatocellular carcinoma

Author	Number of resections	Child-Pugh A (%)	Cirrhosis (%)	Major resections (%)	Operative time (min)	Blood loss (mL)	Conversion to open approach (%)	R0 (%)	Mortality (%)	Morbidity (%)	Hospital stay (days)
Lai *et al.*[23]	42	NA	82.9	23	229.4 (m)	412.6 (M)	4.8	93	0	7.1	6.2 (m)
Di Sandro *et al.*[39]	10	100	NA	0	236 (M)	220 (M)	0	100	0	0	6.8 (M)
Lai and Tang[40]	100	NA	80	27	207.4 (m)	334.6 (m)	4	96	0	14	7.3 (m)
Magistri *et al.*[13]	22	90.9	68.2	9.1	318 (m)	400 (m)	0	95.5	0	68.2	5.1 (m)
Chen *et al.*[41]	81	NA	26.2	41.9	343 (M)	282 (M)	1.6	100	0	4.9	7.5 (M)
Wang *et al.*[42]	63	93.9	NA	4.8	296 (m)	206 (m)	0	93.7	0	11.1	6.2 (m)
Khan *et al.*[43]	34	NA	31.4	32.3	246 (M)	125 (M)	8.8	94	0	35.2	4 (M)
Zhu *et al.*[44]	140	NA	48.6	12.6	NA	NA	19	100	0	30.4	NA
Lim *et al.*[45]	44	90.9	61.4	11.4	252 (m)	NA	4.5	NA	0	36.4	9 (m)
Balzano *et al.*[46]	40	NA	97.5	0	217.5 (M)	NA	7.5	90	0	25	6 (M)
Zhang *et al.*[47]a	113	84.1	31	37.2	205 (M)	150 (M)	2.7	100	1.8	8.8	6 (M)
Zhu *et al.*[48]	56	89.3	NA	10.7	220 (M)	200 (M)	14.3	98.2	0	12.5	6 (M)
Duong *et al.*[50]b	123	NA	NA	NA	NA	NA	8.1	NA	0.8	NA	3 (M)

[a]The study focuses on elderly patients (≥ 65 years); [b]Data obtained from the National Cancer Database; m: mean; M: median; NA: not applicable.

Importantly, all the studies comparing RLR to OLR reported similar oncological outcomes in terms of survival and negative margin rates while confirming the longer operative time and shorter length of stay after RLR[42,43,47,49].

Zhu *et al.*[48] prospectively collected data on 369 patients with BCLC stage 0-A HCC who underwent curative liver resection for HCC using OLR, LLR, or RLR and analyzed outcomes after propensity score matching. In both LLR and RLR, the operative time and duration of Pringle's maneuver were significantly longer than those in the OLR group, while the length of stay was shorter. No significant differences in the 5-year DFS (63.8%, 54.4%, and 50.6%) or OS rates (80.8%, 78.6%, and 75.7%, respectively) were appreciated among the three groups.

ROBOTIC *VS.* LAPAROSCOPIC APPROACH

A case-matched analysis by Di Sandro *et al.*[39] showed reduced blood loss (P = 0.03) and increased operative time (P = 0.04) among ten patients who underwent RLR for HCC *vs.* LLR, while short and long-term results were similar in the two groups.

Interesting results were published by Lai *et al.*[40], who noted a higher proportion of major hepatectomies (27% *vs.* 2.9%; P = 0.002) and tumors located in posterosuperior segments (29% *vs.* 0%; P < 0.001) in the RLR *vs.* LLR group. The robotic approach was associated with a significantly longer mean operative time (207.4 *vs.* 134.2 min; P = 0.001). Both groups had similar blood loss (334.6 *vs.* 336 mL; P = 0.99), morbidity (14% *vs.* 20%; P = 0.42), and mortality rates (0% *vs.* 0%). There was no difference in terms of R0 resection rate (96% *vs.* 91.4%; P = 0.72), 5-year OS (65% *vs.* 48%; P = 0.28), and DFS (42% *vs.*38%; P = 0.65). The main limitation of this study was the number of patients analyzed (100 RLRs *vs.* 35 LLRs).

Another retrospective study on HCC resection performed robotically and laparoscopically[13] demonstrated that there was an increase in Clavien-Dindo I-II level complications and pleural effusion among patients undergoing LLR (P = 0.03, P = 0.01, respectively). The open conversion rate was higher among LLR patients (P = 0.046), yet operative time was higher among RLR patients (P < 0.01). There was no difference in length of stay (P = 0.15).

Later it was reported[45] that there was a lower rate of R1 status and anatomical resection rate for patients who underwent RLR in comparison to LLR after propensity score matching (3% *vs.*15%, P = 0.09; 36% *vs.* 61%, P = 0.049). While there was an increase in 3-year OS and a decrease in recurrence among patients who underwent RHR for HCC, the results were not statistically significant (P = 0.27, P = 0.26, respectively).

A retrospective comparative analysis by Balzano *et al.*[46] showed a higher use of Pringle's maneuver (32.7% *vs.* 20%; P = 0.23) and a shorter duration of surgery (median of 165.5 *vs.* 217.5 min; P = 0.04) in LLR *vs.* RLR. Incidence of complications (25% *vs.*32.7%; P = 0.49), blood transfusions (2.5% *vs.*9.6%; P = 0.21), and median length of stay (6 *vs.* 5; P = 0.54) were similar between RLR and LLR. One and 5-year OS and DFS were 100% and 79%, and 95% and 26% for RLR *vs.* 96.2% and 76.9%, and 84.6% and 26.9% for LLR (P = 0.65 for OS and 0.72 for DFS).

Finally, a matched analysis from the National Cancer Database found an improved OS after RLR *vs.* LLR (HR: 0.64 and 95%CI: 0.43%-0.96% for intent-to-treat; HR: 0.59 and 95%CI: 0.39%-0.90% for end-treatment). In this series, RLR had a significantly higher conversion rate and median hospital stay than LLR. Nevertheless, no data were available on underlying liver disease or type of surgery; thus, it was not included in the propensity score matching[50].

Table 2 summarizes the studies comparing RLR and LLR for HCC. To try to assess if there is an actual advantage in RHR over LRR, Murtha-Lemekhova *et al.*[51] performed a review of the literature and meta-analysis, comparing a total of 324 RLRs and 613 LRRs. The rate of major liver resections was higher in the RLR group (P = 0.006), and no differences were noted in terms of operative (P = 0.49) and Pringle (P = 0.11) time and length of stay (P = 0.77). While there was no difference in the overall rate of postoperative complications (P = 0.28), Clavien-Dindo III-IV level complications were more frequent after LLR (P = 0.05). The odds of developing postoperative liver failure (P = 0.24), ascites (P = 0.35), bile leak (P = 0.78), hemorrhages (P = 0.66), and infections (P = 0.84) were similar in both groups. R0 was more frequently achieved with RLR (P = 0.041), but recurrence rates (P = 0.12) and OS (P = 0.769) were comparable. The authors summarized how RLR is non-superior to LLR, with no proven advantage in cirrhotic patients.

LIMITATIONS

When comparing RLR to other surgical approaches, the main limitation is the lack of randomized clinical trials, a small number of patients analyzed in the available studies, heterogeneity of reported results, and inconsistent use of propensity score matching. Secondarily, none of the reviewed papers mentioned outcomes such as functional activity, pain levels, quality of life, costs, and financial burden. Nevertheless, it must be noted how limited data regarding cost is controversial. While a study on RLR (not specifically focused on HCC) reported an overall economic advantage[52] and no differences in terms of total surgical supply[53], a later report found higher costs with RLR[54].

Table 2. A summary of papers comparing outcomes after robotic and laparoscopic liver resection for hepatocellular carcinoma. The table shows whether outcomes were statistically significantly higher, lower, or equal when the robotic approach was compared to the laparoscopic one, considering several parameters

Author	Child-Pugh A	Cirrhosis	Major resections	Operative time	Blood loss	Conversion to an open approach	R0	Mortality	Morbidity	Hospital stay	RFS	OS
Lai *et al.*[23]a	NA	NA	NA	↑	=	NA	=	=	=	NA	NA	NA
Di Sandro *et al.*[39]	=	NA	=	↑	↓	NA	=	=	=	=	NA	NA
Lai *et al.*[40]	NA	=	↑	↑	=	=	=	=	=	=	=	=
Magistri *et al.*[13]	=	↓	=	↑	=	↓	=	=	↓	=	NA	NA
Lim *et al.*[45]	=	=	=	=	↑	=	=	=	=	=	=	=
Balzano *et al.*[46]	NA	=	=	↑	=	=	=	=	=	=	=	=
Zhu *et al.*[48]	=	NA	=	=	=	NA	=	=	=	=	=	=
Duong *et al.*[50]b	NA	NA	NA	NA	NA	↑	NA	=	NA	↑	NA	↑

[a]Subgroup analysis: robot-assisted laparoscopic minor liver resection (< 3 Couinaud segments) *vs.* conventional laparoscopic minor liver resection; [b]Data obtained from the National Cancer Database; NA: not applicable.

Today, some of the remaining challenges with robotics are as follows:

(1) Specialized robotic training is required for surgeons and the assisting healthcare team to perform a RLR properly and safely. While simulation and virtual reality training have been proven to prepare surgeons with robotic skills, there is limited standardization in training within surgical residency programs[27,55];

(2) Devices specific to parenchymal transection of the liver are limited, and sophisticated suction devices that the operators can control by themselves are lacking[27,56];

(3) RLR frequently requires increased intraoperative time, as demonstrated, which may contribute to increased hospital costs[54].

CONCLUSION

In this review, the role of robotic surgery for HCC is detailed. The evidence consistently demonstrates overall comparable short- and long-term results to LLR. Achieving R0 resection in hard-to-reach anatomic locations, increased intraoperative maneuverability, and the ability to utilize surgical-enhancing technologies - like 3D reconstruction and ICG - to achieve safe and effective resection are important driving factors in the adoption of robotic techniques in HCC surgery. Moreover, the current innovations under development will lead to a wider diffusion of RLR, the development of advanced image processing technologies, haptic feedback, liver-specific devices, lower cost, and more robot choices. These innovations cumulatively will lead to safer RLR for our patients.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study: Panettieri E
Made significant contributions to the writing of the manuscript: Chirban A, Hansen B
Contributed to the production of the final draft and gave administrative, technical, and material support: Vega EA, Conrad C

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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