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REVIEW ARTICLE

Robotic Surgery for Malignant Liver Disease: a Systematic Review of Oncological and Surgical Outcomes

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Abstract

Robot-assisted laparoscopic surgery is yet another modification of minimally invasive liver surgery. It is described as feasible and safe from the surgical point of view; however, oncological outcomes need to be adequately analysed to justify the use of this technique when resecting malignant liver tumours. We reviewed existing English medical literature on robot-assisted laparoscopic liver surgery. We analysed surgical outcomes and oncological outcomes. We analysed operative parameters including operative time, type of hepatectomy, blood loss, conversion rate, morbidity and mortality rates and length of stay. We also analysed oncological outcomes including completeness of resection (R status), recurrence, survival and follow-up data. A total of 582 patients undergoing robot-assisted laparoscopic liver surgery were analysed from 17 eligible publications. Only 5 publications reported survival data. The overall morbidity was 19% with 0.2% reported mortality. R0 resection was achieved in 96% of patients. Robotic liver surgery is feasible and safe with acceptable morbidity and oncological outcomes including resection margins. However, well-designed trials are required to provide evidence in terms of survival and disease-free intervals when performed for malignancy.

Keywords Liver resection · Robotic surgery · Hepatectomy · Laparoscopy

Introduction

Minimally invasive surgery is already established as the gold standard for many surgical procedures [1, 2]. A step further is robot-assisted laparoscopic surgery which provides several inbuilt advantages including a three-dimensional view and a wider range of movements at the tip of the instruments. Robotic surgery therefore has gained wide acceptance in difficult laparoscopic approaches and has unequivocally demonstrated benefit in highly specialized surgery such as prostatectomy and rectal resections in terms of reduced blood loss and transfusion requirements [3, 4].

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Laparoscopic liver surgery has been implemented progressively over a more prolonged period of time, probably due to the difficult access, complex anatomy and difficult dissection when transecting the liver parenchyma. Despite all these factors, minimally invasive surgery for liver resections has been demonstrated to be feasible and safe in expert hands [5]. Part of the development of the minimally invasive approaches for liver surgery is the use of the robotic systems. Robot-assisted laparoscopic surgery has been successfully used for liver resection for several years and it is considered currently as a feasible and safe approach [6, 7].

Experience in this surgery is limited to a few centres worldwide and small case series. Additionally, oncological and long-term outcomes have not been adequately analysed. The aim of the current review is to analyse the outcomes of robot-assisted laparoscopic surgery in liver resections for malignant diseases.

Methods

Two independent authors (RDN and SV) performed a literature search (PubMed/MEDLINE and EMBASE) for

originally published studies on robotic liver resection from January 1990 until December 2018. Used search terms included major MeSH terms "liver/hepatic neoplasm", "Robot assisted liver resection", "Robot assisted hepatectomy", "Robot assisted laparoscopic liver resection", "Robot assisted laparoscopic hepatectomy" and "robotics" in addition to the search phrases "robotic liver resection" OR "robotic hepatic resection" OR "robotic hepatec*", "robotic surgery", "hepatectomy" and "liver resection".

All titles and abstracts were reviewed. Clearly irrelevant titles, duplicated series and case reports were excluded. Small cases series with fewer than 10 malignant cases reported were excluded as were single-centre series reporting duplicate data in separate manuscripts. Only studies reporting oncological data (at least one parameter on surgical margins or survival) were included in the analysis. Gallbladder cancer and hilar cholangiocarcinoma were excluded.

Demographic patient data (age, gender) were analysed along with American Society of Anaesthesiologists physical status classification (ASA grade) [8], body mass index (BMI) and indication for liver resection. Main surgical details collected were the type of resection, surgical technique, operative time, estimated blood loss and requirements for intraoperative transfusion, use of liver inflow occlusion, type of parenchymal transection, conversion rate, type of conversion and reason for conversion. Major hepatectomy was defined as any resection involving the removal of more than 3 contiguous liver segments. Minor liver resection was defined as the removal of 3 or fewer contiguous liver segments [9]. Main collected outcomes were postoperative mortality, percentage of optimal surgical resection (R0 resection based on "Residual Tumour classification" [10]), postoperative complications (collected based on Clavien-Dindo classification for surgical complications [11]), length of stay, recurrence rate, overall survival (OS) and disease-free survival (DFS). Post hepatectomy liver failure (PHLF) was defined using ISGLS criteria [12].

Results

An initial literature search identified 2888 papers from which 73 eligible manuscripts were subsequently selected for detailed review. Finally, 17 studies were included for data extraction and analysis (Fig. 1) [13–28]. A total of 704 patients were included in this series for both benign and malignant diagnoses whilst there is reported data on 582 patients with malignant liver disease.

Patient demographic data is illustrated in Table 1. Mean age is 58.7 years old. Only 10 studies reported on ASA grade and 6 studies reported on BMI (range 16.7–45). The commonest indication for liver resection was HCC (45%), followed by colorectal liver metastases (CRC) (36%). The types of resection

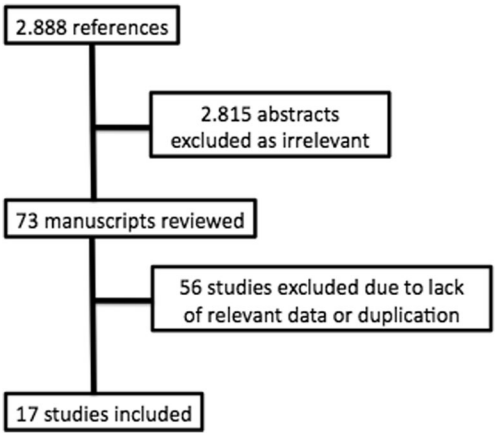

Fig. 1 Search and manuscripts flow chart

reported included any type of hepatectomy from wedge resections and segmentectomies to right trisectionectomies (Table 2).

Most reported series had a mix of benign and malignant diseases. Mean operative time was 277 min for all procedures. The mean blood loss was estimated at 250 ml (from negligible to a maximum of 3500 ml). Some series reported on the use of inflow occlusion during liver resection with a very variable range of times (from 0 to 166 min of occlusion time). There were a wide variety of instruments used for the parenchymal transection including ultrasonic and harmonic scalpels, diathermy and vascular staplers. Mean length of stay was 6.3 days ranging from 1 to 46.

Overall morbidity was 19% (135 patients) including all complications (grades 1–4 of Clavien-Dindo classification [11]). There were 3 cases reported of urinary bladder injury [30, 31]. There were 2 cases of postoperative mortality (0.2%) in the whole series.

Oncological outcomes, either from the surgical point of view or long-term results, are summarised in Table 3. Overall R0 resection rate was 96%. Only two of the studies reported an R0 resection rate inferior to 90% and there were no cases of R2 resection. Four of the 17 case series reported a 100% R0 resection rate. In 6 of the total 582 patients included in this analysis, conversion to an open procedure was required to maintain the oncological nature of the procedure (Table 2) [17, 29]. Only five papers analysed survival for their patients including OS and DFS for the different indications (HCC and CRC) (Table 3).

Discussion

This review illustrates the present position of robotic liver surgery. As most of the studies have concluded, robotic liver resection is feasible and safe. However, long-term data for oncological outcomes including overall survival and disease-free survival is still lacking [11, 32]. This may partly be due to the fact that robotic liver surgery is a recent development, and

Table 1 Series and main demographic data

Author	Centres	Period	N	Age, mean (range)	Gender (male/female)	ASA grade	BMI
Choi et al. [16]	Single	Nov 2008–Apr 2011	30 (21 malignant)	52.4*	14/16	NR	NR
Tsung et al. [26]	Single	Nov 2007–Dec 2011	57 (40 malignant)	58.3*	24/33*	Median 3 85% > 3	16 pp. BMI < 25 41 pp. > BMI 25*
Giulianotti et al. [29]	2 centres (one surgeon)	March 2005–Jan 2010	24 (17malignant)	55 (21–84)	10/14	NR	NR
Troisi et al. [25]	2 centres	Mar 2008–Mar 2012	40 (28 malignant)	64.6	27/13	NR	NR
Spampinato et al. [23]	2 centres	Jan 2009–Dec 2012	25 (16 malignant)	63 (32–80)*	13/12*	80% 2	Median 24
Tranchart et al. [24]	Single	Jan 2008–Apr 2013	28 (15 malignant)	66.5*	15/13	23 (82%) > 2	26.1 (16.7–36)
Yu et al. [28]	Single	May 2010–Oct 2011	13 (10 malignant)	50.4	7/6*	NR	NR
Gulianotti et al. [17]	2 centres (one surgeon)	Mar 2002–Mar 2009	70 (42 malignant)	60 (21–84)*	30/40*	57 pp. > ASA 2	NR
Casciola et al. [13]	Single	Jan 2008–Sep 2010	23 (19 malignant)	66.4 (32–84)*	15/8*	50% ASA 3	27.7 (19–38.3)
Chandarana et al. [15]	Single	Jun 2015–Oct 2016	25 (11 malignant)	52 (32–84)*	13/12*	NR	23.8
Ceccarelli et al. [14]	Single	Sep 2012–Dec 2016	70 (47 malignant)	67 (25–89)*	NR	22% ASA = 3–4	NR
Montalti et al. [22]	Single	NR	36 (24 malignant)	62 (32–84)*	21/15*	35% ASA 3	NR
Kingham et al. [18]	Single	2010–2014	64 (47 malignant)	64 (40–91)*	32/32*	94% ASA 1	26 (17–45)
Marino et al. [21]	Single	Apr 2015–May 2017	35	63 (42–77)	22/13	25% ASA > 2	23.5 (18–27)
Wang et al. [27]	Single	Jun 2013–Jul 2016	63	NR	43/20	NR	NR
Lai et al. [19]	Single	1998–2015	95	62.1	66/29	NR	NR
Lee et al. [20]	Single	2010–2015	70 (52 malignant)	58 (20–82)	46/24	9% ASA > 2	NR

*Data reported for the full series of patients including benign and malignant diseases. *NR* not reported. *BMI* body mass index. *ASA* American Society of Anaesthesia

Table 2 Main operative data

Author	Operation time	Type of resection (major/minor)	Blood loss (mL), mean (range)	Conversion rate	Reason for conversion	Morbidity	Mortality	Length of stay in days
Choi et al. [16]	507*	20/10	343 (95–1500)	2 (6.7%)	Bleeding and difficulty	13 (43.3%)*	0	11.7*
Tsung et al. [26]	253 (180–355)*	21/36	200 (50–337)*	4 (7%)*	Bleeding and difficulty	11 (19.3%)*	0	4 (3–5)
Giulianotti et al.	337 (240–480)	24/0	457 (100–2000)	1(4%)	Adhesions + oncological reasons	6 (25%)	0	9 (3–23)
Troisi et al. [25]	271*	0/40	330*	8 (20%)*	Bleeding	12.5%	0	6.1
Spampinato et al. [23]	430 (240–725)	24/2	250 (100–1900)	1 (4%)*	NR	5 (20%)	0	8 (4–22)
Tranchart et al. [24]	210 (45–480)	0/28	200 (0–1800)	4*	2 bleeding, 1 adhesions 1, no progression	5 (17%)*	0	6 (1–15)*
Yu et al. [28]	291.5	3/10	388	0	NA	0	0	7.8
Gulianotti et al. [17]	270*	27/43	262 (20–2000)*	4 (5.7%)	1 bleeding, 3 oncological reasons	15 (21.4%)	0	7 (2–26)
Casciola et al. [13]	280 (150–420)*	0/30	245 (0–1000)*	2 (8.6%)*	Length of procedure	7 (30.1%)	0	8.9 (3–46)
Chandarana et al. [15]	219	1/10	150 (50–3500)*	5 (12%)*	Duodenal perforation, bleeding and oncological concerns.	NR	0	4 (2–21)
Ceccarelli et al. [14]	115 (80–290)*	NR	25 (5–350)*	8 (11%)*	Bleeding	8 (11.4%)	0	3 (1–8)
Montalti et al. [22]	306 (53–790)	All minor	415 (0–1500)	5 (13%)*	Bleeding, oncological concerns and adhesions	13 (36%)	0	4
Kingham et al. [18]	163 (56–480)	6/59*	100 (10–1700)	4 (6.3%)*	NR	10.9%	2 (3%)*	4 (1–25)
Marino et al. [21]	315 (200–445)	All major	245 (125–628)	2 (5.7%)	Bleeding	6 (17%)	0	6.5 (5–17)
Wang et al. [27]	296	All minor	206	0	NA	7 (11%)	0	6.2
Lai et al. [19]	207	27/75	334 (5–3500)	5 (5%)	NR	19 (19%)	0	7.3
Lee et al. [20]	251 (97–620)	14/56*	100 (2–2500)	4 (5%)	NR	8 (11.4%)	0	5 (2–22)

*Data reported for the full series of patients including benign and malignant diseases. *NR* not reported

Table 3 Oncological data

Author	Diagnosis	R0	R1	R2	Recurrence	Survival	Follow-up
Tsung et al. [26]	7HCC, 21CLM, 11 others	29 (97.5%)	1 (2.5%)	NR	NR	NR	NR
Giulianotti et al. [29]	11 CLM, 4NonCLM, 1HCC, 1Hepatoblastoma	16 (94.2)	1 (5.8)	0	2/11 CLM, 1/1 pheocrom	NR	34
Troisi et al. [25]	24 CLM, 3HCC, 1CCa	90%	3 (10%)	0	1yDFS for CLM 79% and 3yDFS for CLM 62%	9.6	NR
Spampinato et al. [23]	11 CLM, 2 HCC, 2 CCa, 1 metastasis from anal carcinoma	100%	0	0	NR	NR	NR
Yu et al. [28]	10 HCC	100%	0	0	NR	NR	NR
Gulianotti et al. [17]	13 HCC, 16CLM, 2 CCa, 3GB Ca, 1 hepatoblastoma, 7 NonCLM	100%	0	0	NR	NR	NR
Casciola et al. [13]	14 CLM, 3 HCC, 2 NonCLM	85%	3 (15%)	0	3 (15%)	NR	25.1
Chandarana et al. [15]	11 Primary liver tumours	100%	0	0	NR	NR	NR
Ceccareli et al. [14]	22CLM, 12HCC, 1CCa	94.3%	2 (5.7%)	0	NR	NR	NR
Montalti et al. [22]	21 CLM, 3HCC, 1CCa	88%	3 (12%)	0	DFS for CLM 73%, 46% and 4 6% for 1, 3 and 5 years	OS CLM 92%, 64% and 40% for 1, 3 and 5 years	NR
Kirgham et al. [18]	32CLM, 12 primary liver tumours	97.8%	1 (2.2%)	0	NR	NR	NR
Marino et al. [21]	14CLM, 18HCC, 3CCa	94%	2 (6%)	0	3 years DFS 65%	3 years OS 86%	NR
Wang et al. [27]	63 HCC	94%	4 (6%)	0	DFS 77.8%, 71.9% and 71.9% for 1, 2 and 3 years	OS 100%, 97.7% and 97.7% for 1, 2 and 3 years.	NR
Lee et al. [20]	40 HCC, 8CLM, 3CCa, 1 other.	98.2%	1 (1.8%)	0	NR	NR	NR
Lai et al. [19]	95HCC	96%	4 (4%)	0	5 years DFS 42%	5 years OS 65%	26

NR not reported, *HCC* hepatocellular carcinoma, *CLM* colorectal liver metastasis, *CCa* cholangiocarcinoma, *DFS* disease free survival, *OS* overall survival

most case series are small and have included a mix of benign and malignant pathology.

Even where malignant cases have been analysed, the group is heterogeneous and hence no definite analysis of oncological outcomes has been done. Furthermore, most papers have focussed on immediate postoperative outcomes, with respect to morbidity and conversion aspects of robotic surgery. Hence, oncological and survival data has not been included in the majority of these publications.

The main surgical outcomes are properly described in all the included studies. The cumulative data demonstrated that there was a 0.2% reported mortality from robotic liver surgery. All the studies but one report no mortality. No mortality is of the greatest value but we understand that it might be related to the small cohort of patients and case selection. This data should be contrasted in the future, as, in case of confirmation, a reduction in the surgical mortality would promote the use of this surgical approach.

Reduction of the intraoperative blood loss is the most commonly reported advantage for robotic surgery [3, 4]. Most papers comparing robotic versus laparoscopic and/or open surgery agree that there is a significant reduction in blood loss in favour of the robotic approach. Benefits of reducing the amount of blood loss not only affect the actual haemodynamic response but also minimise the needs for transfusion and the associated risks. Data from this review suggests that this assessment is also applicable to robotic liver surgery. There is however limited data on results and the influence of inflow occlusion.

The mean surgical time in the series was 277 min. This is slightly higher than that reported for laparoscopic liver surgery (range 95–280 min) [5]. In this sense, there was no differentiation between a major and minor liver resection and a healthy vs cirrhotic liver. Only one paper described and analysed the data regarding the docking time and console time [33]. It is common knowledge that the perioperative preparation and logistics of robotic surgery, including anaesthetic strategies, increase the operative time. In this sense, the learning curve of this novel approach partially justifies this longer time [29].

Of all the complications reported 73% were minor complications and 27% were major complications, which are comparable to accepted complication rates for liver resection [5, 16]. However, this is the first review where we highlight a complication related only to the surgical approach. The presence of 3 cases of urinary bladder injury is of the most relevant consideration [30, 31]. There is, obviously, nothing reported of this complication in open liver surgery and only some series of laparoscopic pelvic surgery report data on bladder injuries but all of them during the surgical procedure [34, 35]. Gynaecological procedures describe up to 8% of iatrogenic bladder injuries [34] whilst in general surgery procedures such as bowel resections (including rectal resection), it occurred between 0.12 and 0.41% [35]. Robotic liver surgery therefore might represent an increment in the rate of urinary bladder injuries and this data needs to be confirmed. Damage during the specimen extraction could be justified because of the bigger size of the resected specimen as it has been described before during the retrieval of a laparoscopically resected kidney [36].

Appropriate case selection is important for achieving success in a new surgical procedure. Patient body habitus may be shown to create additional difficulties in planning a laparoscopic approach. There is no evidence however of any standard anatomy or physiognomy that could represent a contraindication for any type of surgery whilst there is evidence supporting that obese patients can receive laparoscopic liver surgery safely [37]. However, a more detailed analysis of BMI and its influence on outcomes following robotic liver surgery would be able to provide greater guidance on patient selection.

Only 6 studies were reported on BMI (range 16–40) [13, 23, 24, 26, 32, 33, 38]. This data includes a wide range of values, from 16 to 45, which would support the application of robotic liver surgery to patients irrespective of their BMI. Considering that the concept of robotic surgery is essentially a modification of the traditional laparoscopic approach, it is likely that the influence of BMI on laparoscopic surgery can be applied to the robotic approach and therefore be considered safe. There is however an alternative view put forward by Trachart et al. who concluded that higher BMI can be a risk factor for increased complications in robotic liver surgery [24].

The main outcomes of the current review are those related to the oncological results. Completeness of resection and the presence of negative surgical margins (R0 resection) are possibly the most important prognostic factor determining survival and recurrence following liver surgery and they have demonstrated to be relevant for the patient survival and therefore of the most interest in the full process of treatment [39, 40]. All series have reported on R status following robotic liver resection. Despite the small numbers, the initial results following robotic liver surgery seem equivalent to similar comparisons for open and laparoscopic surgery [5, 40]. Data reported for the long-term survival in terms of DFS and OS is reported separately for CRC and HCC and again is comparable to the literature available. However, well-designed prospective trials are needed to provide stronger evidence.

Special consideration should be given to a recent manuscript published by Khan and colleagues. It is a large retrospective multicentre analysis but it has not been included in the tables as it is a compilation of the multiple centres involved [41]. Most of the data reported the same was already included individually. This review suggests that whilst robotic surgery provides an equal chance as open and laparoscopic liver surgery of obtaining negative margins, no conclusions can be drawn on the long-term overall and disease-free survivals, as data is minimal.

Cost and economic implications of robotic surgery have to be assessed. Two papers reported on the economic data and cost implications [28, 32]. They both report higher costs for the robotic cases. Economic benefit of the minimally invasive approach is not based on the surgical procedure but in facilitating quicker recovery, shorter length of stay and earlier resumption to work. These advantages may thus neutralise and offset the absolute cost of the procedure, which may be higher. The shorter length of stay in the hospital and/or ITU may represent an economic compensation of the more expensive surgical procedure.

In summary, robot-assisted laparoscopic liver surgery for malignant diseases is feasible and safe. Current data suggests that it is an optimal approach for malignant liver tumours in terms of clearance of the resection margins. It may be used and employed in appropriate indications by experienced liver surgeons, trained to perform this procedure. Long-term survival data with respect to its overall oncological safety and efficacy is awaited.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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