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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Robotic Versus Open Hepatectomy for Hepatocellular Carcinoma: A Matched Comparison

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ABSTRACT

Background. Robotic hepatectomy has been suggested to be a safe and effective approach for liver disease; however, studies comparing robotic hepatectomy with the conventional open approach regarding oncologic outcomes for hepatocellular carcinoma (HCC) are limited. Accordingly, we performed a matched comparison of surgical and oncological outcomes between robotic and open hepatectomy.

Methods. Between January 2012 and October 2015, a total of 183 patients underwent robotic hepatectomy and 275 patients underwent open hepatectomy by the same surgical team in our center. Eighty-one newly diagnosed HCC cases in each group were compared under propensity score matching (PSM) in a 1:1 ratio.

Results. With robotic hepatectomy, the conversion rate was 1.6 % and the complication rate was 4.4 %. On PSM, the groups had a comparable percentage of major liver resections (41.9 vs. 39.5 %) and liver cirrhosis (45.7 vs. 46.9 %). Compared with the open group, the robotic group required longer operation times (343 vs. 220 min), shorter hospital stays (7.5 vs. 10.1 days), and lower dosages of postoperative patient-controlled analgesia (350 vs. 554 ng/kg). The 3-year disease-free survival of the robotic group was comparable with that of the open group (72.2 % vs. 58.0 %; $p = 0.062$), as was the 3-year overall survival (92.6 vs. 93.7 %; $p = 0.431$).

Conclusions. This is the first oncological study comparing robotic liver resection for HCC with open resection. Robotic hepatectomy can be applied for challenging major resections in patients with cirrhotic liver disease with less postoperative pain and shorter hospital stays without compromising oncological outcomes.

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The rapid development of minimally invasive techniques has changed the landscape of surgery over the past 20 years. The minimally invasive approach has been reported to have benefits in advanced cancer surgeries[1–4] and the same benefits have been demonstrated in laparoscopic liver surgery, including reduced postoperative pain and decreased length of hospital stays with experienced surgeons.[5–7] However, the limitations of conventional laparoscopic surgery, including reduced visualization, restricted range of motion, and possible physiologic tremors, contribute to the increased complexity of this procedure.[8,9] Furthermore, the complex vascular and biliary anatomy of liver surgery creates a precipitous learning curve when dealing with fragile parenchyma, difficult exposures, and the risk of bleeding.[10,11] Therefore, the proportion of major laparoscopic hepatectomies was limited to approximately 16 % of all attempts in a worldwide case study,[12] and the progression of minimally invasive liver resection has been relatively slow in comparison with other surgical procedures. Moreover, the minimally invasive approach for hepatocellular carcinoma (HCC) is facing the same situation, for most studies included small lesions and minor hepatectomies.[13]

The robotic surgical system has potential advantages of instrument flexibility, three-dimensional surgical version, and stability.[14,15] The robotic hepatectomy procedure allows for safety and feasibility,[16–18] and major liver resections can be performed by a purely minimally invasive approach with the assistance of the robotic system.[19] However, although the advances in this platform have overcome some of the limitations of the conventional laparoscopic operation, robotic liver resection remains one of the last relative barriers in robotic surgery, especially in cirrhotic livers.[20,21] In fact, open liver resection has always been the standard approach for liver cancer, and surgeons have been reluctant to adopt robotic liver resection due to uncertain oncological outcomes.[22,23] In this study, PSM was utilized to compare the perioperative and survival outcomes for patients with newly diagnosed HCC who underwent either a robotic or open hepatectomy by a single surgical team in the same period.

PATIENTS AND METHODS

This was a retrospective review of previously collected data. All procedures were approved by the institution's supervisory committee, and this study was approved by the Institutional Review Board. From January 2012 to October 2015, patients with primary, newly diagnosed HCC were selected for this study, with the exclusion of patients who had undergone a previous operation, percutaneous radiofrequency ablation, or transarterial chemoembolization. Patients with a combined cholangiocarcinoma on pathologic results or initial presentation of distant metastasis were also excluded. The diagnosis of liver cirrhosis was based on tissue diagnosis using Ishak's score (≥ 5). Using these criteria, 81 constitutive newly diagnosed HCC patients who underwent a robotic procedure were compared with the same population of patients who underwent open hepatectomy during the same period, performed by the same surgical team, by using PSM. In addition, 41 patients who were newly diagnosed with HCC underwent laparoscopic hepatectomy and were enrolled from our previous study, in which 69 laparoscopic hepatectomy cases were performed between December 2007 and December 2011.[19]

The types of liver resections were adopted according to the Brisbane 2000 classification.[24] The surgical plans were consistent in both the robotic and open hepatectomies, and anatomical resections were performed for patients with good estimated residual liver function on the indocyanine green test. Surgeons attempted to allow a 1 cm gross margin during tumor resection in both groups, with a positive resection margin being defined as the presence of tumor cells at the line of transection due to microscopic involvement of the main tumor, venous permeation, or microsatellite nodules.

Patients who fit the selection criteria based on the Louisville statement,[25] with tumors <10 cm in size, were given the option of undergoing minimally invasive surgery (MIS). Patients were at will to have an MIS hepatectomy after they discussed the surgical risk with our team. The MIS procedure was performed as a conventional laparoscopy between 2007 and 2011, and has been performed as robotic surgery since 2012. Other selection criteria for hepatectomy included Child's class A liver function, curatively treatable HCC without major vessel invasion, and stable cardiopulmonary function. By using the patient positioning and robotic settings described in our previous report,[19] the open liver resection was performed with similar techniques, including individual vascular clipping and bipolar coagulation for hemostasis. The Pringle maneuver was not performed in either group, and individual inflow control at the hilum was performed in a manner similar to major open hepatectomies.

Postoperative pain was controlled with intravenous opioid drugs, and then shifted to oral pain medications as tolerated by the patient. For patients who chose a patient-controlled analgesia (PCA) system for initial postoperative pain control, the PCA device was used to control pain for 3 days after the operation. Postoperative complications were recorded and classified according to the Clavien–Dindo system.[26] Additionally, ambulation was encouraged, beginning on the first postoperative day if the patient tolerated the pain, and patients were only discharged after proper recovery of liver function and return of general function were confirmed.

All patients were followed monthly for the first year following the operation and then quarterly if no recurrence was detected. Imaging studies, including computed tomography or abdominal ultrasonography, were performed within 2 months after the operation, then quarterly in the first year and semi-annually thereafter. Recurrence was diagnosed by the presence of diagnostic findings on computed tomographic scan, magnetic resonance imaging, or, if necessary, with tissue sampling.

Statistical Analysis and Propensity Score Matching

The following covariates were matched: age, sex, hepatitis profile, underlying hepatopathy (e.g. liver dysfunction, cirrhosis), and tumor size. The propensity score analysis and matching were performed using the PSM program through the SPSS R-Plugin (IBM SPSS version 22; IBM Corporation, Armonk, NY, USA), which utilizes a newly written R code,[27] as described by Thoemmes.[28] Analyses utilized single nearest-neighbor matching, with no replacement (a single participant could not be selected multiple times). The baseline characteristics of patients were expressed as median (range). The two-sided Student's t test was used to compare continuous variables, and a χ^2 test was used to compare discrete variables. Survival analysis was performed using the time of disease-free survival versus recurrence of a tumor or death. Survival curves were computed using the Kaplan–Meier method, and were compared between groups using the log-rank test. Significance was defined as $p < 0.05$. All statistical calculations were made using the IBM SPSS statistics software for Windows (IBM Corporation).

RESULTS

A total of 183 patients underwent pure robotic hepatectomy during the study period; the overview of our robotic procedures is presented in Table 1. During the study period, 81 and 160 patients with newly diagnosed HCC underwent a robotic or open hepatectomy, respectively, as illustrated in Electronic Supplementary Table 1. With PSM, 81 newly diagnosed HCC patients who underwent robotic resection were compared with 81 open hepatectomy cases. No significant preoperative characteristic differences were noted between the groups, including hepatitis profiles, preoperative liver function tests, and tumor size. The robotic group contained a similar proportion of patients with liver cirrhosis when compared with the open group (46.9 vs. 45.7 %) (Table 2). In addition, patients who underwent robotic hepatectomies had pathological results, including cancer stage and histology grade, similar to those who underwent open procedures.

Neither group showed the occurrence of major complications (Table 3). The robotic group had four (4.9 %) cases of minor complications, including one case of chest infection, one case of infectious biloma, one case of bile leak, and one episode of bleeding. In contrast, the open group had one case of wound infection and three cases of bile leaks. The robotic procedure had a longer operation time compared with the open group (343 vs. 220 min; $p < 0.001$), although total blood loss was not significantly different between the groups (282 vs. 263 mL; $p = 0.724$). Robotic procedures required less total administration of PCA on postoperative day 1 when compared with open procedures (350 vs. 554 ng/kg; $p < 0.001$). Additionally, these patients resumed ambulation earlier and had a significantly shorter length of hospital stay (7.5 vs. 10.1 days; $p = 0.001$). The disease-free survival rate for robotic procedures was 91.5 % at 1 year, 84.3 % at 2 years, and 72.2 % at 3 years. This result is comparable with open procedures, with 79.2 % at 1 year, 73.0 % at 2 years, and 58.0 % at 3 years (Fig. 1a; $p = 0.062$). The overall survival rate in the robotic group (1-year, 100 %; 2-year, 97.8 %; 3-year, 92.6 %) was not significantly different from that of patients in the open group (1-year, 98.4 %; 2-year, 93.7 %; 3-year, 93.7 %; $p = 0.431$) (Fig. 1b).

Major hepatectomy was defined as a liver resection of three or more contiguous Couinaud segments. Major robotic hepatectomy was performed in 34 (42 %) patients, while 32 (40 %) patients underwent a major open resection (Table 4). The blood loss associated with the major robotic procedure was less than that of the open operation (182 vs. 322 mL; $p = 0.026$), along with less need for postoperative pain control and shorter hospital stays (8.9 vs. 12.3 days; $p = 0.017$). No patients required blood transfusions during the major robotic liver resections, while three patients (9 %) needed blood transfusions during the major open hepatectomies. Additionally, no major complications developed after either type of major procedure, and the minor complication rate (5.9 vs. 6.3 %) was comparable between the groups.

Because of the bias of surgical experience in the different periods of time, the data of the robotic and laparoscopic groups should not be analyzed for statistical significance. In our center, the surgical team accumulated experience with laparoscopic hepatectomy between 2007 and 2011, and then started to develop robotic hepatectomy beginning in 2012. However, our data implied that robotic hepatectomy dealt with more major hepatectomy cases than laparoscopic hepatectomy (41.9 vs. 9.8 %) [Electronic Supplementary Table 2], and had a longer operation time (343 vs. 228 min), a lower conversion rate (0 vs. 12.2 %), and comparable blood loss and complication rates (4.9 vs. 9.8 %). The medical cost for the robotic and laparoscopic groups was US$6885 and US$3560, respectively.

DISCUSSION

The adoption of MIS major liver resection in clinical practice has been gradual,[29] and the worldwide trend has increased slowly, from 16 to 22 % during the last 5 years.[12,30] In our center, the surgical team accumulated experience with laparoscopic hepatectomies from 2007 to 2011, and then began to develop robotic hepatectomy in 2012. The comparison between the robotic and laparoscopic groups was not statistically evaluated because of the bias of surgical experience in the different periods; however, as previously outlined,[19,31] our robotic approach has generally dealt with more major hepatectomies. Of note, in our experience, the robotic procedure has demonstrated a similar blood loss and complication rate compared with the laparoscopic procedure. Despite the learning curve associated with minimally invasive hepatectomies, the robotic group had a lower conversion rate, even though patients who underwent a robotic hepatectomy experienced longer operation times and the burden of higher medical costs.

Although a minimally invasive approach for HCC has been documented with feasibility and safety, most studies

TABLE 1 Characteristics of patients undergoing robotic hepatectomy [$n = 183$]

Age, years [median (range)]	60.8 (22–89)
Sex (male/female)	118/65
Cirrhosis	48 (26.2)
Disease	
Malignancy	123 (67.2)
HCC	112 (91.0)
Cholangiocarcinoma	5 (4.2)
Liver metastasis	4 (3.2)
Other[a]	2 (1.6)
Benign	60 (32.8)
Living-related liver donor	15 (25.0)
Focal nodular hyperplasia	14 (23.3)
Hemangioma	10 (16.7)
Hepatolithiasis	6 (10.0)
Cystic tumor	6 (10.0)
Other[b]	9 (15.0)
Procedures	
Minor	91 (49.7)
Left lateral sectionectomy	39 (42.9)
Anterior segmentectomy	31 (34.1)
Posterior segmentectomy	21 (23.0)
Major	92 (50.3)
Right hepatectomy	41 (44.6)
Left hepatectomy	32 (34.8)
Right trisectionectomy	6 (6.5)
Left trisectionectomy	3 (3.3)
Trisegmentectomy 8-5-4	10 (10.8)
Operation time, min [median (range)]	361 (102–805)
Blood loss, mL [median (range)]	249 (50–2250)
Transfusion	10 (5.5)
Conversion	3 (1.6)
Patients with complications	8 (4.4)
Clavien–Dindo I and II	4
Clavien–Dindo III and IV	3
Clavien–Dindo V	1
Overall survival, months [median (range)]	23.4 (1–41)
Length of hospital stay, days [median (range)]	7.5 (2–41)

Data are expressed as n (%) unless otherwise specified

HCC hepatocellular carcinoma

[a] Angiosarcoma, 1; combined hepatocellular carcinoma and cholangiocarcinoma, 1

[b] Angiomyolipoma, 3; adenoma, 3; biliary intrahepatic neoplasm, 1; epithelioid tumor, 1; regenerative nodule, 1

evaluated small lesions and minor hepatectomy.[13] Conversely, the high proportion of major hepatectomies among our robotic liver surgeries, and the relatively significant differences when compared with open major hepatectomies, indicate that robotic major liver resection offers potential advantages, including less blood loss, less postoperative pain, earlier ambulation, and shorter hospital stays when compared with open surgery. Furthermore, recent consensus statements recommend that laparoscopic hepatectomies in cirrhotic patients be reserved for experienced centers.[25,32] In this series, the prevalence of liver cirrhosis in the robotic group was similar to that of the open

TABLE 2 Pathological results of the newly diagnosed hepatocellular carcinoma on propensity score matching

	Robotic group [$n = 81$]	Open group [$n = 81$]	p value
Cirrhosis	37 (45.7)	38 (46.9)	0.875
Margin			0.028[a]
Margin involved	0	0	
Margin not involved, mm			
<1	2 (2.5)	1 (1.3)	
1–10	26 (32.1)	39 (48.1)	
10–20	31 (38.3)	34 (41.9)	
>20	22 (27.1)	7 (8.7)	
Histology grade[b]			0.565
Low	42 (51.9)	43 (53.1)	
High	39 (48.1)	38 (46.9)	
Tumor capsule			0.357
Well encapsulated	18 (22.2)	18 (22.2)	
Partially encapsulated	39 (48.1)	48 (59.3)	
No capsule	24 (29.7)	15 (18.5)	
Tumor necrosis	35 (43.2)	34 (41.9)	0.985
Gross vascular invasion	0	2 (2.5)	0.157
Microvascular invasion	23 (28.4)	25 (30.9)	0.692
Satellite nodules	3 (3.7)	7 (8.6)	0.143
TNM stage			0.357
I	54 (66.7)	55 (67.9)	
II	25 (30.9)	20 (24.7)	
III	2 (2.4)	6 (7.4)	
IV	0	0	

Data are expressed as n (%)

TNM American Joint Committee on Cancer Tumor-Node-Metastasis, 7th edition

[a] Statistical significance at $p < 0.05$

[b] Edmondson–Steiner grading

group. In fact, liver cirrhosis was not an exclusion criterion for our robotic liver resections, and the introduction of the robotic system has admittedly provided a platform to overcome some limitations of conventional laparoscopy, with the potential advantages of instrument flexibility, stability, and three-dimensional version. It is not surprising that the robotic group required a significantly longer operation time than patients who underwent open procedures, which was partially owing to the requirement to dock the robot, exchange instruments,[33,34] and dissect delicately under magnified views.

Since the open procedure has remained the standard treatment of HCC, comparing oncological outcomes is always required for new approaches. In this matched study, the robotic and open liver resections for HCC were compared based on preoperative liver function tests and tumor size. Furthermore, performance of procedures by a single surgeon reduced potential variability due to surgical skill and procedure planning. All patients in both groups achieved an R0 resection with similar cancer staging, with no significant differences noted in the pathological results or histologic grades between the groups. To our knowledge, this is the first study to compare oncological outcomes for robotic versus open liver resections in newly diagnosed HCC cases, which should provide more solid conclusions since the selection criteria of previous studies were not as rigorous. During follow-up, the robotic surgery group showed no difference in disease-free survival or overall survival compared with the open group. As mentioned in a previous report regarding minimally invasive hepatectomies,[35] the robotic group had a trend towards a better disease-free survival; however, the differences did not have statistical significance and the contributing factors should be evaluated with more data and experience.

Our experience with robotic hepatectomy should not be considered as suggesting that a robotic platform is a

TABLE 3 Operation details and short-term outcomes of the newly diagnosed hepatocellular carcinoma on propensity score matching [$n = 81$]

	Robotic group	Open group	p value
Procedure			
Major hepatectomy[a]	34 (41.9)	32 (39.5)	0.841
Right-sided hepatectomy[b]	15	13	
Left-sided hepatectomy[c]	14	5	
Trisegmentectomy 8-5-4	5	14	
Minor hepatectomy	47 (58.1)	49 (60.5)	0.898
Left lateral sectionectomy	12	1	
Anterior segmentectomy	25	19	
Posterior segmentectomy	10	29	
Operation time, min [median (range)]	343 (140–715)	220 (88–505)	<0.001[d]
Blood loss, mL [median (range)]	282 (50–2200)	263 (50–1100)	0.724
Blood transfusion	6 (7.4)	3 (3.7)	0.496
Hospital stay, days [median (range)]	7.5 (3–26)	10.1 (5–42)	0.001[d]
Patients with complications			
Clavien–Dindo classification			
I	0	1 (1.2)	0.981
Wound infection	0	1	
II	4 (4.9)	3 (3.7)	0.317
Chest infection	1	0	
Infectious biloma	1	0	
Bile leak	1	3	
Bleeding	1	0	
III	0	0	–
IV	0	0	–
V	0	0	–
VPS on POD 1	3.4	3.2	0.666
Total PCA/BW on POD 1, ng/kg	350	554	<0.001[d]
First ambulation day [median (range)]	1.5 (1–2)	1.8 (1–3)	0.063
VPS on the first ambulatory day	1.4	1.5	0.611
Total PCA/BW during initial ambulation	320	521	0.015[d]

Data are expressed as n (%) unless otherwise specified

VPS average pain score, *POD* postoperative day, *PCA* patient-controlled analgesia, *BW* bodyweight

[a] Hepatectomy for three or more contiguous Couinaud segments

[b] Right hepatectomy and right trisectionectomy

[c] Left hepatectomy and left trisectionectomy

[d] Statistical significance at $p < 0.05$

shortcut for MIS major hepatectomy. Although we found a trend of a higher proportion of major hepatectomy in the robotic group, the confidence of facing the challenge comes from not only the assistance of robotic instruments but also our experience of laparoscopic hepatectomy. Regarding the learning curve, we presented an overview of our robotic experience and the evolution of MIS in our institute. A dual-console system should be considered to facilitate real-time education and practice under experienced supervisors; however, a complete analysis of the learning curve and surgical pitfalls should be addressed carefully to help surgeons sharpen their surgical performance. Moreover, further studies should be undertaken to overcome the aforementioned limitations. More accurate records of the patients' characteristics, selection criteria, and intraoperative and postoperative outcomes should be collected in prospective studies. Multicenter studies are required to overcome the limitations of a single-institution study.

CONCLUSIONS

Robotic hepatectomies should be limited to experienced surgeons with extensive training in both open and minimally invasive liver surgery. Our data suggest that HCC

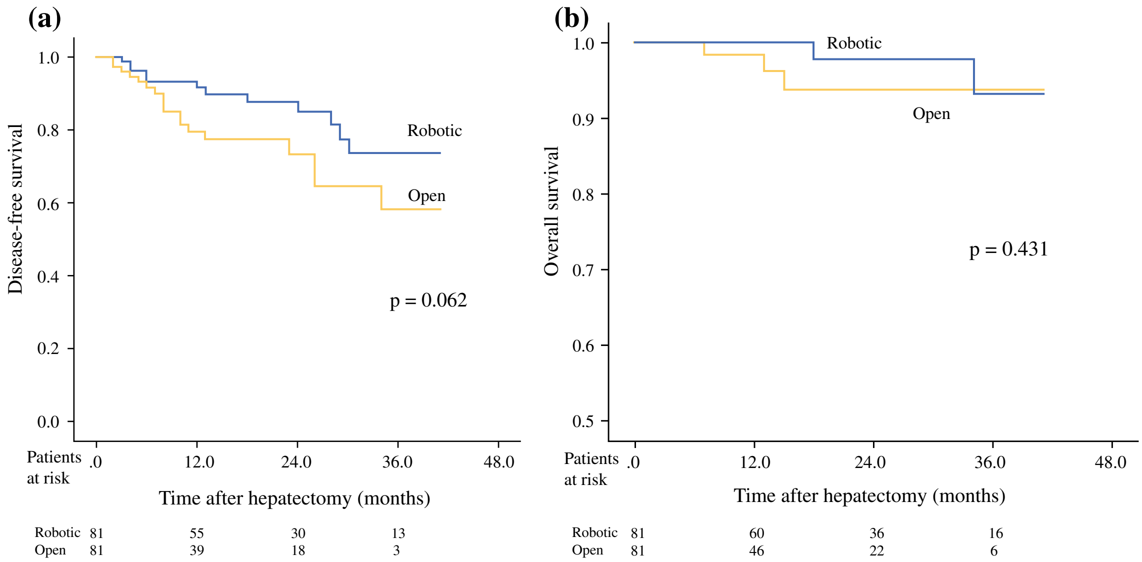

FIG. 1 Oncologic results between robotic and open hepatectomies for hepatocellular carcinoma. **a** The disease-free survivals of the two groups at 3 years were 72.2 and 58.0 %, respectively ($p = 0.062$). **b** The overall survivals of the two groups at 3 years were 92.6 and 93.7 %, respectively ($p = 0.431$)

TABLE 4 Operation details and short-term outcomes of major hepatectomy of the newly diagnosed hepatocellular carcinoma on propensity score matching

	Robotic group [$n = 34$]	Open group [$n = 32$]	p value
Operation time, min [median (range)]	402 (169–715)	285 (217–505)	<0.001[a]
Blood loss, mL [median (range)]	182 (50–800)	322 (50–1100)	0.026[a]
Blood transfusion	0	3 (9.4)	0.239
Total postoperative PCA/BW, ng/kg	649	1084	0.004[a]
Hospital stay, days [median (range)]	8.9 (5–26)	12.3 (6–42)	0.017[a]
Patients with complications			
Clavien–Dindo I and II	2 (5.9)	2 (6.3)	0.317
Clavien–Dindo III, IV and V	0	0	–

Values are in median (range)/(percentage)

Major hepatectomy hepatectomy for three or more contiguous Couinaud segments, *PCA* patient-controlled analgesia, *BW* body weight

[a] Statistical significance at $p < 0.05$

patients in need of a major hepatectomy may benefit from a robotic approach. However, the procedure costs remain an important issue, and more experience should be accumulated to understand the true advantage and disadvantage of the platform. In terms of safety and feasibility, robotic liver resections for HCC have demonstrated comparable outcomes to the open approach, and the robotic platform allows the potential for performance of more complex major hepatectomies.

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CONFLICTS OF INTEREST None.

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