Robotic Liver Resection For Hepatocellular Carcinoma. Analysis of Surgical Margins and Clinical Outcomes From A Western Tertiary Hepatobiliary Center

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Research Article

Keywords: Robotic Hepatectomy, Hepatocellular Carcinoma, Tumor Distance to Margins

Posted Date: June 17th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1758374/v1

Abstract

Background

This study was undertaken to determine surgical outcomes of patients undergoing robotic hepatectomy for hepatocellular carcinoma (HCC) and to investigate the correlation between tumor distance to margin and perioperative outcomes, as well as overall survival (OS). To our knowledge, this study represents the largest series of robotic liver resection for HCC in North America.

Methods

We retrospectively analyzed 58 consecutive patients who underwent robotic liver resection for HCC. Patients were further stratified by tumor distance to margin (≤ 1mm, 1.1-9.9mm, ≥ 10mm) and their clinical outcomes including OS were compared.

Results

A majority of patients attained a greater than 1mm tumor distance to margin (81%). There were no differences in tumor size between patient cohorts who attained ≤ 1mm, 1.1-9.9mm, and ≥ 10mm margins. There were no differences in pre-, intra-, and postoperative outcomes among the three cohorts. Cost variables of interest were also similar. OS was highest in the > 10mm margin cohort, and this was statistically significant at 3 and 5 years.

Conclusion

Robotic HCC resection was associated with adequate tumor distance to margin. Wide margins ≥ 10mm is associated with the best OS.

Introduction

Hepatocellular Carcinoma (HCC) is the most common primary liver malignancy worldwide. There is an increasing incidence of HCC in the United States in the last decade, in part due to the obesity epidemic, which is gradually replacing hepatitis C and alcohol abuse as the cause of liver parenchymal damage[2]. Long standing obesity leads to Non-Alcoholic Steatohepatitis (NASH) and cirrhosis, the major risk factor for the development of HCC. In patients with preserved liver function (Child-Pugh A class), surgical resection provides the best chance for a cure given the continued scarcity of liver donors.

Since the advent of minimally invasive liver surgery, an increasing number of patients have benefitted from curative liver resection. Laparoscopic approaches are applied mostly in cases of minor and anterolaterally located peripheral tumor resection. Due to the inherent limitations of straight instrumentation in conventional laparoscopy, the robotic approach has become increasingly adopted to overcome some of these technical limitations. Currently, there has been a rise in robotic application in HCC resection, which provides ambidextrous instrumentation, superior 3-dimensional visualization, and easy suturing in difficult locations, while maintaining the benefits of an expeditious perioperative recovery attained via small incisions. Well-performed minimally invasive liver resection enhances perioperative recovery and expands the pool of surgical candidates by improving the risk to benefit ratio. Nonetheless, the operation must remain oncologically adequate to effect a cure. While oncological data on open and laparoscopic resections have been published, data regarding surgical margins after robotic liver resection for HCC is very limited. This is in part because few centers in the US have an adequate number of patients treated via the robotic approach. Many surgeons are hesitant to offer minimally invasive resections for HCC because the background liver parenchyma is often cirrhotic, making it more technically challenging to handle and resect.

At our tertiary hepatobiliary referral center, we have accumulated a substantial experience in robotic HCC resection since late 2016, the year of inception of our formal robotic liver program. We sought to publish our perioperative and long-term outcomes of patients undergoing robotic HCC resection, with a particular focus on resection margin distance and overall survival (OS), to critically examine the role robotic approach plays in obtaining adequate resection margins. We hypothesize that, the robotic approach leads to adequate oncological resection margins and subsequently long-term OS, while providing excellent short-term perioperative outcomes.

Materials And Methods

Data Source and Inclusion Criteria

With IRB approval, we analyzed a total of 58 consecutive patients who underwent robotic hepatectomy for treatment of HCC between 2016 and 2022. The relationships between the tumor distance to margins and perioperative data were determined using regression analyses. Patients who underwent hepatectomy for benign, other primary liver cancer, or metastatic liver tumors were excluded from the study. Patients not undergoing curative intent hepatectomy for HCC were also excluded.

The robotic approach is our preferred method and uniformly offered. Our current contraindications that exist to offering robotic liver surgery to our patients is the clear need for a major vascular resection (Inferior vena cava, portal vein, and hepatic artery) and reconstruction based on preoperative imaging (triphasic computed tomography or magnetic resonance imaging scan), in which case an open approach is offered. Absolute size of the lesion does not necessarily affect our decision to pursue a robotic approach. Although pneumoperitoneum can have effects on perioperative cardiopulmonary physiology, we rarely find this to be a discriminating factor in regards to surgical approach since adequate cardiopulmonary resilience and endurance are also required to tolerate and recover from a major open hepatectomy. A history of prior abdominal operations or even a prior hepatectomy does not constitute a major contraindication and it has recently been shown to be safe to proceed with a robotic approach in this setting.

To measure the level of technical difficulty in minimally invasive liver resection, in our liver surgery program we adopted the IWATE score. It is a widely accepted Japanese 4-level classification system involving six preoperative factors (tumor location, size, proximity to major vessels, extent of resection, use of hand assistance, and liver function). Each patient in this study was assigned an IWATE score to reflect individual operative difficulty.

Study Variables

The following factors were studied: sex, age, body mass index (BMI), history of prior abdominal operations, American Society of Anesthesiology (ASA) class, Model of End-stage Liver Disease (MELD) score, Childs-Pugh Score, IWATE score, tumor size, operative duration, estimated blood loss (EBL), conversion to open, intraoperative complications, 90-day postoperative complications, resection margin distance, overall length of stay (LOS), 90-day mortality, readmission within 30 days, and OS. Patients who attained positive margins were grouped in the ≤ 1mm margin group.

Operative duration was defined as the time from the first skin incision to the placement of the final dressing. Intraoperative complications were defined as any event necessitating major deviations from the planned procedure. Postoperative complications that significantly impacted the patients' clinical progress, as defined by a post-operative event that increased their LOS by more than one standard deviation above the mean, were compiled together as a single outcome variable. The Clavien-Dindo Classification (CDC) system was used to grade the severity of the postoperative complications. For illustrative purposes, data are presented as median (mean ± SD). Statistical significance was accepted at $p \leq 0.05$.

Operative technique

A detailed description of our operative technique has been described in other publications , , . Starting from 2016, we began to utilize the Intuitive Surgical Inc. da Vinci® Robotic Platform (Intuitive Surgical, Sunnyvale, CA, USA) to undertake minimally invasively hepatobiliary resections. The following is our institutional approach to robotic liver surgery.

Patients are positioned supine on the operating table and induced with general endotracheal anesthesia. Reverse Trendelenburg (15°) with a slight left/right tilt (5°) position is applied depending on the type of resection. The da Vinci Xi® robotic surgical system is docked over the patient’s right should and paired with the operating table to allow for intra-operative bed motion. An 8 mm trocar is inserted through the umbilicus for the robotic camera. Two 8 mm robotic ports are utilized at the right and left midclavicular lines in parallel. The latter is upsized to a 12mm port as needed for robotic stapling. A fourth 8 mm robotic port is placed along the left anterior axillary line at the level of the umbilicus. Finally, an Advanced Access Gelport® (Applied Medical, Rancho Santa Margarita, CA, USA), placed between the right midclavicular line and the umbilicus, is used for bedside suctioning and specimen extraction (Fig. 1). An AirSeal® (ConMed, Utica, NY, USA) port is inserted through the Gelport for insufflation and smoke evacuation. The bedside assistant, usually a board-certified general surgeon participating as a fellow in our hepatopancreatobiliary surgery training program, stands to the right of the patient, opposite from the scrub nurse (Fig. 2).

The operation begins with adequate liver inspection after taking down the falciform ligament all the way to the hepatocaval confluence. A thorough search for peritoneal carcinomatosis and occult hepatic metastasis is performed by a careful videoscopic inspection of the peritoneal surface including the liver capsule, followed by an intraoperative liver ultrasonography. Identified liver tumors determined resectable are marked and transected superficially using a robotic monopolar cautery, as guided by ultrasonography, taking care to note of any major portal or hepatic venous branches. Cephalad retraction of the liver is performed by a non-grasping bowel grasper to expose the porta hepatis and to gain inflow vascular control. A combination of bipolar energy forceps, vessel sealer, Hemolock clips, 4 – 0 prolene sutures completes the deeper parenchymal transection. Cavitron ultrasonic surgical aspirator (CUSA) is not used in our robotic liver resection; neither is Pringle maneuver routinely utilized. When a formal hemihepatectomy is undertaken, the ipsilateral hepatic artery and portal vein are dissected individually and ligated using 3 – 0 silk sutures and Hemolock clips, before the liver parenchyma is split. Robotic staplers are used to transect the corresponding bile duct pedicle at the level of hilar plate and ultimately to transect the hepatic vein close to its inferior vena cava (IVC) junction. Once the specimens are detached, they are placed in an extraction bag and removed via the Gelport® incision. Frozen section examination is performed for all resected specimens to confirm R0 resection. The surgeon accompanies the specimen to the pathologist and a concordant measurement of the resection margin is first conducted grossly and on frozen section samples; the specimen then undergoes Formalin-Fixed Paraffin-Embedded (FFPE) evaluation with a high-definition microscope by two independent hepatobiliary pathologists.

Statistical Analysis

Data was maintained on an Excel (Microsoft Corporation Redmond, WA) spreadsheet and analyzed using GraphPad InStat version (3.0) (GraphPad Software La Jolla, CA). Statistical tests performed where appropriate were: F-test, Mann-Whitney U test, Student’s T-test, and Fisher’s exact test. Kaplan Meier analysis was used to estimate overall survivals. Statistical significance was accepted with 95% probability. For illustrative purposes, data are presented as a median (mean ± standard deviation).

Results

Fifty-eight patients met the inclusion criteria. There were 11, 25, and 22 patients who attained ≤ 1mm, 1.1-9.9mm and ≥ 10mm tumor to distance margin after robotic hepatectomy for HCC. There were no statistically significant differences in any preoperative variables of note between the three margin cohorts. Collectively, our patients demonstrated the following characteristics: age 67(66 ± 12.2) years old, men (66%), BMI 28(29 ± 8.2), ASA 3, MELD 9, Child-Pugh Class A. A history of a prior abdominal operation existed in 38% of patients. A majority of the patients had an advanced or expert level IWATE score lesion (84%), with expert level being the most common (45%). IWATE score did not statistically significantly differ between the margin cohorts.

There were no statistically significant differences in any intraoperative variables between the three margin cohorts. Collectively our patients endured an operative duration of 247(274 ± 95.0) minutes, 200(271 ± 247.6) ml of EBL, two conversions to open and no intraoperative complications. Tumor size was 4(5 ± 2.8) cm; this also did not differ between the margin cohorts.

There were no statistically significant differences between the three margin cohorts in any postoperative variables. Collectively our patients had two Clavien-Dindo Classification > 3 complications, two 90-day mortalities and a length of stay of 4(5 ± 4.6) days. There were 7 readmissions within 30 days (Table 1).

Table 1
Robotic HCC Resection Margin Analysis Clinical Variables of Interest

	≤ 1mm	1.1mm-9.9mm	≥ 10mm	Total	P-Values
Number of Patients	11	25	22	58	
Age (years)	77(71 ± 14.4)	66(66 ± 12.1)	66(65 ± 10.9)	67(66 ± 12.2)	0.80
Sex (M/W)	7/4	18/7	13/9	38/20	0.71
BMI (kg/m2)	27(29 ± 9.1)	28(29 ± 10.2)	28(28 ± 5.1)	28(29 ± 8.2)	0.90
Prior Abdominal Operation	4(36%)	9(36%)	9(41%)	22 (38%)	0.64
ASA	3(3 ± 0.5)	3(3 ± 0.5)	3(3 ± 0.5)	3(3 ± 0.5)	0.17
MELD Score	10(12 ± 6.1)	9(10 ± 4.4)	8(9 ± 2.4)	9(10 ± 4.3)	0.15
Childs-Pugh Score	5(6 ± 1.3)	5(5 ± 0.8)	5(5 ± 0.8)	5(5 ± 0.9)	0.94
IWATE					
Low (0–3)	1(9%)	0(0%)	0(0%)	1(2%)	0.41
Intermediate (4–6)	0(0%)	3(12%)	5(23%)	8(14%)	
Advanced (7–9)	6(55%)	9(36%)	8(36%)	23(39%)	
Expert (10–12)	4(36%)	13(52%)	9(41%)	26(45%)	
Intraoperative Variables					
Operative Duration (min)	239(271 ± 125.2)	246(265 ± 71.6)	271(285 ± 104.6)	247(274 ± 95.0)	0.25
Estimated Blood Loss (mL)	150(325 ± 458.9)	200(251 ± 197.1)	250(268 ± 140.6)	200(271 ± 247.6)	0.86
Conversions to Open (n)	0(0%)	1(4%)	1(5%)	2(3%)	0.83
Intraoperative Complications (n)	0(0%)	0(0%)	0(0%)	0(0%)	0.47
Tumor Size (cm)	5(6 ± 3.3)	4(5 ± 2.6)	5(6 ± 2.9)	4(5 ± 2.8)	0.36
Postoperative Variables					
Clavien-Dindo Score (≥ III)	1(V)	1(V)	0(0%)	2(V,V)	0.18
90-day Mortality (n)	1(9%)	1(4%)	0(0%)	2(3%)	0.18
Length of Stay (days)	4(7 ± 6.5)	4(5 ± 5.2)	3(4 ± 2.1)	4(5 ± 4.6)	0.10
Readmissions within 30 days (n)	1(9%)	4(16%)	2(9%)	7(12%)	0.77

Cost analysis identified no difference in expenditure or any financial variable of note between the three margin cohorts. Collectively, total costs were $28,895(39,571 ± 49,886.03) for a reimbursement of $15,281(32,402 ±

40,092.91) resulting in a contribution margin of $-13,128 (7,170 ± 42,516.10) to the hospital (Table 2).

Table 2
– Cost of Robotic Hepatectomy for Hepatocellular Carcinoma

Tumor Distance to Margin	**≤ 1mm**	**1.1–9.9 mm**	**≥ 10mm**	**Combined**	**p value**
Total Cost	$28,588(30,343 ± 12,830.19)	$28,400(47,626 ± 73,131.64)	$27,961(32,408 ± 14,602.09)	$28,895(39,571 ± 49,886.03)	0.99
Variable Cost	$17,796(18,635 ± 9,089.14)	$18,805(31,123 ± 49,392.94)	$19,609(21,259 ± 10,269.14)	$19,295(25,674 ± 33,762.31)	0.93
Fixed Direct Cost	$2,358(2,592 ± 1,159.79)	$2,096(3,728 ± 4,603.87)	$2,161(2,233 ± 804.18)	$2,138(2,688 ± 2,528.49)	0.77
Fixed Indirect Cost	$9,789(9,710 ± 3,680.93)	$8,180(13,821 ± 20,584.46)	$7,888(8,876 ± 3,816.90)	$8,369(11,155 ± 13,775.92)	0.91
Hospital Reimbursement(s) Received	$17,036(26,889 ± 30,143.29)	$15,307(32,007 ± 45,931.94)	$12,986(33,718 ± 37,959.28)	$15,281(32,402 ± 40,092.91)	0.60
Contribution margin	-$8,717(-3,453 ± 26,083.36)	-$14,787(-15,619 ± 49,334.95)	-$11,948(-1,310 ± 39,046.85)	$-13,128(-7,170 ± 42,516.10)	0.63

Kaplan-Meier survival analysis identified a superior OS in patients who attained greater tumor distance to margin (p = 0.013) (Fig. 3). Estimated mean OS was greatest in the ≥ 10mm cohort, intermediate in the 1.1-9.9mm cohort and shortest in the ≤ 1mm cohort at 1 year from resection (88% vs 84% vs 70%, p = 0.26), at 3 years from resection (88% vs 47% vs 35%, p = 0.033) and at 5 years from resection (88% vs 47% vs 24%,p = 0.013) (Table 3). In this series, the length of follow-up varied from 12 to 80 months.

Table 3 - Overall Survival				
		At One Year	At Three Years	At Five Years
Margin Group	≤1 mm	70%	35%	24%
	1.1-9.9 mm	84%	47%	47%
	≥10 mm	88%	88%	88%
p-value		0.26	0.033	0.013

Discussion

Data on the oncologic adequacy and perioperative outcomes of robotic HCC resection is limited, particularly from the United States. Prior studies have not raised the issue of resection margin distance[3,,,], which has become a topic of important debate in the era of minimally invasive liver surgery, since many surgical oncologists are still skeptical of the oncological outcomes after laparoscopic or robotic liver resection. Robotics, perhaps due to superior degrees of freedom over laparoscopy, can reduce the need for an unplanned conversion to an open approach, which can have an impact on OS. In addition to the current literature, which demonstrates acceptable short and long-term perioperative outcomes after robotic HCC resection[6], data justifying the robot approach from a resection margin standpoint is required. The majority of published western reports only consist of small case series with < 50 patients[16]. To our knowledge, this study represents the largest single-center series of robotic liver resection for HCC in North America, contributing the most substantial data yet.

This study complements the nascent but growing research evaluating robotic approaches to HCC resection, especially in the western countries where HCC is far less common compared to Asia. Satisfactory perioperative outcomes, OS and resection margins were demonstrated via the robotic approach, suggesting this modality a promising strategy in HCC resection. Aforementioned oncologic concerns seem to be unfounded. Despite a lack of tactile feedback, even challenging posterosuperior lesions can be safely resected robotically while leading to low postoperative complications, decreased ICU utilization, and a short overall LOS.

HCC recurrence after hepatectomy significantly deteriorates long-term OS. The issue of HCC recurrence was explained by the cone unit concept, thus many experts favor anatomical liver resection[3] since non-anatomical resection is associated with an increased recurrence. HCC uniquely spreads intrahepatically via portal and hepatic venous tributaries, resulting in malignant thrombosis in advanced disease[3]. Margin widths greater than those demanded in other hepatic malignancies are required to reduce recurrence, particularly when anatomical resection is infeasible. It is important to recognize that HCC can also manifest as a multicomponent or multifocal lesion whose peripheral microsatellite elements can involve resection margins. Lastly, the remnant cirrhotic parenchyma is also a fertile bed for de novo carcinogenesis, potentially confounding true recurrence.

The multitude of factors driving HCC carcinogenesis has contributed to a widely varying suggestion for an ideal margin, from 5-20mm. Margin width importance rises with lymphovascular invasion, microsatelliting tumors, and high PET-avidity. Conversely, narrower margins are acceptable for ‘early-onset’ lesions and those lacking microvascular invasion. Few studies have demonstrated findings to the contrary and those that do appear to suffer from data heterogeneity.

Our study demonstrated a statistically significant survival advantage in those who attained adequate margins beyond 1 mm with 88% OS up to 5 years. A large majority of our patients attained pathologic true negative margins; at least 81% had ≥ 1.1 mm margins, suggesting that the robotic platform leads to an oncologically adequate hepatectomy and excellent long-term OS.

Collectively, margin width plays a significant role and should be harvested proportional to the HCC biology, its vascular invasive patterns and hepatic segmental anatomy. With the robotic platform, adequate margin width can be attained as this study has demonstrated. We hope it and subsequent studies after it will enrich the current knowledge as we gain more experience and data with robotic HCC resections.

The limitations of this study include a relatively small sample size without randomization nor comparison with an open cohort. It is methodologically difficult to propensity match patients between robotic and open approaches due to the inherent difference in case complexity. At this time, we believe demonstrating the technical and oncologic feasibility of robotic HCC resection is a good first step toward multi-institutional randomized prospective trials. We were unable to obtain adequate data on DFS, due to the decentralized and variant nature of the electronic medical records used by our referring providers. However, this can be indirectly examined, since HCC recurrence presents the most common cause of cancer-specific mortality to patients after HCC resection. The superior OS associated with superior margin acquisition likely reflects a corresponding superior DFS.

Conclusion

Our study is the first of its kind to analyze the effect of the robotic approach to resection margin distance in HCC, and the role it plays in OS. Our finding demonstrates that application of the robotic system in HCC resection can produce an adequate tumor distance to margin, while providing the known benefits of minimally invasive surgical technique. A randomized study is needed to further investigate these critical issues.

Declarations

Funding: No funding was received for conducting this study.

Conflicts of interest: Emanuel Shapera, Kaitlyn Crespo, Cameron Syblis and Iswanto Sucandy have no conflicts of interest. Sharona Ross, Alexander Rosemurgy: Have an educational and research (financial) relationship with Intuitive Surgical Inc. (Intuitive Corporation, Sunnyvale, CA).

Authors contributions: Emanuel Shapera, Kaitlyn Crespo, Cameron Syblis, Sharona Ross, Alexander Rosemurgy and Iswanto Sucandy have contributed to the concept & design of the study, the analysis of data, revision of content, acceptance of final version. The authors agree to be accountable to paper’s contents.

Availability of data and material: Data is available by authors upon reasonable request

Ethics approval: Obtained by IRB approval

Consent to participate: Retrospective study. All patients in clinic signed an agreement to permit data collected to be utilized in a non-identifiable fashion to promote learning, care and research.

Consent for publication: All authors listed above give full consent for manuscript to be published

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Figures

Figure 1

See image above for figure legend.

Figure 2

Figure legend not available with this version.

Figure 3: Kaplan-Meier Curve of Overall Survival

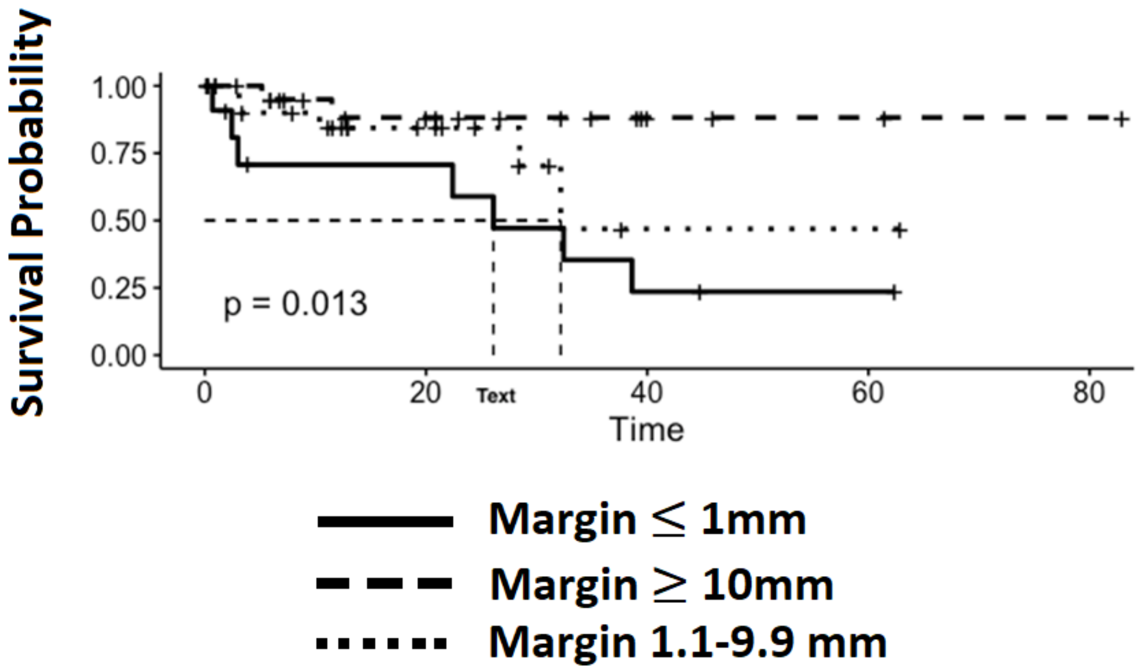

Figure 3

See image above for figure legend.