ORIGINAL ARTICLE

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Total robotic ALPPS approach for hepatocellular carcinoma in cirrhotic liver

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Abstract

Background: Hepatocellular carcinoma (HCC) is a common indication for associating liver partition with portal vein ligation for staged hepatectomy (ALPPS). Robotic liver resection has been done for HCC, but robotic ALPPS is a rare procedure. **Methods:** To present three cases of totally robotic ALPPS in cirrhotic patients with HCC.

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Results: Three cirrhotic male patients with HCC underwent ALPPS; the mean age was 54.3 years. MELD score was \leq 9 and tumour size between 90 and 140 mm. The mean hypertrophy of the future liver remnant after the first stage was 77.5% and no postoperative liver failure was reported. Mean operative time of stage 1 was 7:30 h and of stage 2 was 4:37 h, without blood transfusion. The mean hospital stay for the first stage was 10 days and for the second stage was 9.3 days. No postoperative complication was recorded.

Conclusions: Robotic ALPPS in cirrhotic patients with HCC is safe and feasible.

KEYWORDS

ALPPS, cirrhosis, hepatocellular carcinoma, minimally invasive surgery, morbidity, robotic ALPPS

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) occurs mainly in patients with chronic liver disease or cirrhosis and is one of the most common cancers around the world.¹ Liver transplantation or complete tumour resection are the only means to achieve long-term survival. According to Milan criteria, liver transplantation is indicated for patients with a single tumour ≤ 5 cm or up to three tumours ≤ 3 cm in size each. Surgical resection is indicated by some protocols for patients with tumour of any size, Child-Pugh class A, MELD (Model for End-Stage Liver Disease) score ≤ 9 , without portal hypertension or extra hepatic disease.¹

Associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) results in a greater liver hypertrophy in a shorter period of time. This procedure is indicated in patients with very small future liver remnant (FLR) or after failure of portal vein embolization.¹⁻⁴ According to the first report of the international ALPPS registry, HCC is the second most common indication and Vennarecci et al. observed that HCC was the main indication for ALPPS procedure in their institution, with acceptable overall and disease-free survival.^{5,6}

Laparoscopic ALPPS has been performed since 2012⁷ only in few centres and has shown promising results with lower morbidity rate associated to reduced surgical severity when compared with





FIGURE 1 Docking and trocars disposition (da Vinci Si platform): (A) demarcation lines and trocars disposition; (B) robot after docking

(B)



open procedure.^{8,9} Robotic liver resection has emerged as a promising approach, mainly for malignant neoplasm including colorectal liver metastases and HCC. A recent review observed that more than 1000 patients underwent liver resection using the robotic approach with acceptable 17.6% of complications and 5.9% of conversion rates. $^{10\mathac{10\mathac{14}}{}}$

The first total robotic ALPPS was performed by Vicente et al.¹⁵ in a 58-year-old female patient with colorectal liver metastases and

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FIGURE 2 Computed tomography of the abdomen. (A) HCC in cirrhotic liver, axial plane; (B) coronary plane image of interstage ALPPS

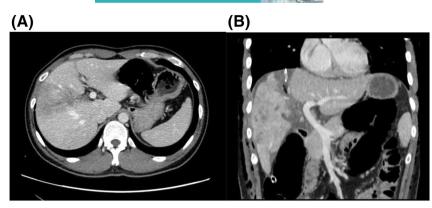


FIGURE 3 Intraoperative image during the parenchymal transection



published in 2015. Then, two other cases of full robotic ALPPS have been published.^{16,17} The precise manipulation of the liver and fine dissection of tissues by robotic approach can minimise the risk of bleeding and biliary fistula, but no difference in morbidity and mortality has been demonstrated so far compared with laparoscopic liver resection. The endo-wristed movements and a high definition by HD and 3-D vision may provide some advantages of robotic approach.¹⁷

We present three cases of patients with HCC in cirrhotic liver who underwent robotic ALPPS procedure.

2 | MATERIALS AND METHODS

From August to October 2019, three cirrhotic male patients with HCC underwent ALPPS at San Lucas Hospital (Rio de Janeiro, Brazil) and University of Modena and Reggio Emilia Hospital (Modena, Italy). Liver deprivation or isolated embolization of hepatic veins was not considered in these cases. The da Vinci Si platform (Intuitive Surgical) was used, and Docking and trocars disposition are presented in Figures 1–3 Non-robotic port was used for stapler. CUSA aspirator was not used for liver transection. Anterior approach was performed without hanging manoeuvre in all patients. The steps of the

procedure can be summarised as follows: Stage 1 (a) intraoperative ultrasound and identification of the resection margins, with a particular focus on hepatic venous drainage; (b) hilar dissection, right portal vein ligation and isolation of right hepatic artery and right biliary duct; (c) complete mobilisation of the right lobe; (d) parenchymal transection (p-ALPPS was performed in case 2 due to intraoperative bleeding) with bipolar forceps clamp crush and harmonic ACE; (e) drain placement. Stage 2 (a) division of right hepatic artery and right biliary duct; (b) in case of p-ALPPS at stage 1 completion of the parenchymal transection; (c) division of middle and right hepatic veins; (d) drain placement.

3 | RESULTS

Case 1

The patient was a 66-year-old man, body mass index (BMI) 22, no portal hypertension, with chronic hepatitis B virus (HBV), presenting with two nodules (segments 5-6: 40 and 90 mm), ASA (American Society of Anesthesiologists) 2, Child A5, MELD 9. The FLR (left lobe) volume was 427 cc (32%) and the total liver volume of 1340.0 cc. The

TABLE 1 Liver function tests after ALPPS (case 1)

| | Stage 1 | | | | Stage 2 | | | |
|------------|---------|-------|-------|------|---------|-------|-------|------|
| | Pod 1 | Pod 3 | Pod 5 | Peak | Pod 1 | Pod 3 | Pod 5 | Peak |
| Bilirubin | 0.66 | 0.53 | na | 0.9 | 0.76 | 0.7 | na | 1.06 |
| INR | 1.42 | 1.18 | na | - | 1.61 | 1.34 | na | - |
| Albumin | na | na | na | - | 2.1 | na | na | - |
| Creatinine | 1.05 | 0.75 | na | - | 0.91 | 0.84 | 0.8 | - |
| AST | 258 | 73 | na | - | 481 | 147 | na | - |
| ALT | 337 | 196 | na | - | 555 | 340 | na | - |

Abbreviations: ALPPS, associating liver partition with portal vein ligation for staged hepatectomy; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

decision to perform robotic right trisectionectomy ALPPS was made after a MDT (Multidisciplinary) tumour board discussion. On stage 1, the liver parenchyma was completely transected and right portal vein was ligated. Operative time was 410 min. The patient received no blood transfusion during the procedure. During the postoperative course, the patient presented arteriovenous fistula with the portal vein and underwent embolization of the right hepatic artery (3a Clavien-Dindo complication).¹⁸ The intensive care unit (ICU) stay was 2 days and hospital stay was 7 days. On postoperative day (POD) 27, the patient underwent a computed tomography (CT) scan and the FLR was 775.0 cc (growth rate 81%). The ALPPS stage 2 was performed 40 days after the first stage, the operative time was 240 min, and on POD 2, he was discharged from the ICU. Liver function tests after stages 1 and 2 are presented in Table 1. The length of hospital stay for the second stage was 8 days. The final pathology confirmed a 3.6- and 8.3-cm HCC R0 margin (4 mm) and cirrhosis was observed in the non-tumoural liver parenchyma. Complications Clavien-Dindo ≥3b was not observed. The last follow up after 7 months, the patient was alive with no signs of recurrence.

Case 2

The patient was a 58-year-old man, BMI 23, presenting with chronic liver disease due to HCV (hepatitis C virus), and a 140 mm nodule in segment 5 of the liver, no portal hypertension. The MELD score was 6, Child-Pugh A5, ASA 3, and alpha fetoprotein (AFP) 2. No portal hypertension was identified. The FLR volume was 29.0% of the left lobe (431.0 cc) and the total liver volume of 1468.0 cc. The case was discussed during the tumour board and decided for robotic ALPPS. On stage 1, the right portal vein was ligated and the liver parenchyma was partially transected (p-ALPPS approach with 80% transection) due to intraoperative bleeding. Operative time was 435 min and the patients received no blood transfusion during the procedure. The ICU stay was 5 days. The postoperative course was uneventful, and on postoperative day 11, the patient underwent a CT scan and a FLR of 734.0 cc was observed (growth rate 70%). The ALPPS stage 2 was performed 13 days after the first stage, the operative time was 310

TABLE 2 Liver function tests after ALPPS (case 2)

| | Stage 1 | | | | Stage 2 | | | |
|------------|---------|-------|-------|------|---------|-------|-------|------|
| | Pod 1 | Pod 3 | Pod 5 | Peak | Pod 1 | Pod 3 | Pod 5 | Peak |
| Bilirubin | 0.46 | 0.3 | 0.33 | 0.93 | 0.54 | 0.39 | na | 0.81 |
| INR | 1.15 | 1.17 | 1.06 | - | 1.18 | 1.26 | na | - |
| Albumin | na | 2.7 | 3.2 | - | 2.2 | 2.0 | na | - |
| Creatinine | 0.97 | 0.83 | 1.19 | - | 0.8 | 0.65 | na | - |
| AST | 310 | 133 | 87 | - | 3,46 | 809 | na | - |
| ALT | 245 | 156 | 107 | - | 2379 | 786 | na | - |

Abbreviations: ALPPS, associating liver partition with portal vein ligation for staged hepatectomy; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

min, and on POD 4, the patient was discharged from the ICU. Liver function tests after stages 1 and 2 are presented in Table 2. The total length of hospital stay was 17 days. The final pathology confirmed a 14 cm HCC but the surgical margin was compromised (R1 margin). The non-tumoural liver parenchyma presented with cirrhosis. No complications Clavien-Dindo \geq 3b was observed. After 7 months of follow up, the patient was alive without signs of recurrence.

Case 3

The patient is a 38-year-old man affected by chronic HBV infection never treated before. Three months before surgery, he started to feel mild pain on the right abdominal flank. An abdominal ultrasonography (US) was performed and revealed a large lesion in the right lobe of the liver. The CT scan confirmed a 7-cm LIRADS 5 (Liver Imaging Reporting and Data System) HCC of the right lobe, with intrahepatic tumour thrombus of a branch of the portal vein for segment VIII. Preoperative AFP was 1417.4 ng/dl, MELD and Child-Pugh scores were 7 and A-5, respectively, and ALBI score was -3,26 (grade 1). Analysis of FLR volume showed 19.6% volume of the left lobe and segment I (233.577 cc and 12.726, respectively; liver total volume of 1254.97 cc; future liver volume/body weight [FLV/BW] ratio, 0.38) with regular indocyanine green clearance (R15, 3.7%; plasma disappearance rate [PDR], 21.9%/min) and no signs of clinically relevant portal hypertension (hepatic venous pressure gradient [HVPG], 2 mmHg). The case was discussed in our multidisciplinary liver tumour board, and a right trisectionectomy ALPPS with full robotic approach (stages 1 and 2) was scheduled. On stage 1, a classic ALPPS was performed, with full thickness parenchymal transection and right portal vein ligation and division. Operative time was 495 min including the table, docking and console time. The postoperative course was uneventful (UCI stay 1 day; hospital stay 3 days), and on POD 8, the patient underwent a CT scan showing a FLR of 37% (575.541 cc on a total of 1547.293 cc; FLV/BW ratio, 0.8). Therefore, he was scheduled for the second stage of ALPPS 10 days after the first surgery. Stage 2 was conducted in a total operative time including table, docking and console time of 280 min, with estimated

TABLE 3 Liver function tests after ALPPS (case 3)

| | Stage 1 | | | | Stage 2 | | | |
|------------|---------|-------|-------|------|---------|-------|-------|------|
| | Pod 1 | Pod 3 | Pod 5 | Peak | Pod 1 | Pod 3 | Pod 5 | Peak |
| Bilirubin | 2.4 | 3.06 | 2.17 | 3.27 | 1.03 | 0.55 | 0.75 | 1.03 |
| INR | 1.82 | 1.3 | 1.08 | - | 1.47 | 1.28 | 1.22 | - |
| Albumin | 2.6 | 3.1 | 3.4 | - | 2.8 | 3.5 | 4.1 | - |
| Creatinine | 0.82 | 0.81 | 0.94 | - | 0.81 | 0.61 | 0.68 | - |
| AST | 2263 | 209 | 56 | - | 308 | 84 | 39 | - |
| ALT | 3971 | 1280 | 549 | - | 324 | 134 | 67 | - |

Abbreviations: ALPPS, associating liver partition with portal vein ligation for staged hepatectomy; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

blood loss of 200 ml. No blood transfusion was necessary during both stages. On POD 1 (ICU), the patient was allowed to drink and eat, and on POD 3, he was discharged in good general conditions. Liver function tests after stages 1 and 2 are presented in Table 3. The final pathology confirmed a 7-cm HCC, G3, microvascular and macrovascular infiltration, tumour thrombus in the branch of the portal vein for segment VIII, R0 margin (12 mm), no satellitosis, necrosis 40% and steatosis 10%. Cirrhosis was confirmed in the non-tumoural liver parenchyma. The last follow up after 8 months the patient was alive with no signs of recurrence.

4 | DISCUSSION

The ALPPS procedure has been demonstrated to promote a greater rate of hypertrophy in a shorter period of time of the FLR compared to conventional portal vein embolization, increasing the possibility of achieving RO resection margin. The initial worldwide enthusiasm was followed by some criticism and intense debate on the morbidity and mortality of the procedure. After that, some modifications were introduced to minimise complications and mortality including partial transection of the liver parenchyma (p-ALPPS) and laparoscopic ALPPS. Portal vein embolization (PVE) and two stage hepatectomy are currently the gold standard in most centres as strategies to increase the FLR. However, PVE is not always feasible in some centres and in cirrhotic liver PVE do not produce an adequate FLR. The second stage in classical two-stage hepatectomy often cannot be performed (35.2%) due to disease progression between stages, insufficient liver regeneration or poor general conditions.¹⁹ In the present study, the patients were not qualified for liver transplantation or single stage resection.^{2,4,6,20} According to Petrowsky et al., partial transection of the liver (50%-80%) was associated with lower postoperative morbidity and mortality with the same volume of the FLR.¹⁹ In cirrhotic patients with HCC, different results have been observed, mainly due to insufficient data about the impact of split on liver hypertrophy in cirrhotic liver. In the present study, partial ALPPS was performed in one patient.²¹⁻²³ As far as we know,

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this is the first series of patients underwent totally robotic ALPPS for HCC in cirrhotic liver.

According to the first report of the international ALPPS registry, liver metastasis from colorectal cancer is the main indication (70%) followed by HCC (8%). The preliminary experience by Vennarecci et al. 6 demonstrated that ALPPS procedure in cirrhotic patients affected by unresectable HCC is feasible and related to satisfying perioperative outcome. The procedure could expand the numbers of patients with Barcelona Clinic Liver Cancer (BCLC) B from chemo-embolization to resection, improving the overall and disease-free survival. In China, ALPPS is accepted in many centres and chronic hepatitis B with large HCC has been the main indication. The time period for hypertrophy can be long in some patients and is related to the severity of fibrosis/cirrhosis or with clinical evidence of portal hypertension (oesophageal varices and splenomegaly). Remarkable hypertrophy has been observed in ALPPS for HCC, even in patients with low-grade fibrosis.²¹⁻²³

In order to minimise the impact of the first stage, some authors have suggested a combination of hanging manoeuvre and anterior approach in cirrhotic patients. This procedure seems to be better performed by robotic approach than laparoscopically and is associated with reduced blood loss and minimal morbidity and mortality.^{21–23}

Schadde et al. observed that MELD score over 10 before stage-2 is an independent predictor of 90-day mortality, in addition to previously defined risk factors. The disease-free at 1 year was 87% and 90-day mortality was 12%.⁶ Adequate liver function in the interstage is crucial for success of ALPPS procedure, being aware of the fact that liver function may be compromised by portal vein ligation and liver transection. In this situation, the stage-2 operation should be deferred to minimise mortality. Anterior approach during the transection can minimise intraoperative blood loss and necessity for blood transfusion. In the present study, the MELD score were ≤ 9 during the interstage.^{22,23}

Laparoscopic approach is associated with lower systemic inflammatory response, resulting in less surgical severity and postoperative pain and early ambulation for the patient. Machado et al. 8 have reported that laparoscopic ALPPS is associated with reduced intraoperative blood loss, less severe postoperative complications and shorter hospital stay when compared with open ALPPS. In this study, ALPPS was performed due to colorectal liver metastases in 86.6% and no HCC in cirrhotic patient was included. A recent study by Melandro et al. 9 identified 15 articles and 26 patients who underwent full minimally invasive ALPPS. Minimally invasive HCC ALPPS was reported in seven patients. Only one case of full robotic ALPPS due to liver metastases from colorectal cancer was reported.^{6,24-28} More recently, a work from the Italian Registry of ALPPS reported that performing at least ALPPS stage 1 with a minimally invasive approach for HCC, either laparoscopic or robotic, is associated with an overall lower risk of postoperative liver failure (PHLF).²⁹ However, the study highlighted a statistically significant difference between open and minimally invasive approach in terms of RO resection, which is consistent with the need for a formal learning curve in laparoscopic and robotic surgery to obtain good oncological results.

After the first full robotic ALPPS by Vicente et al.,¹⁵ four others cases have been performed by Krishnamurthy et al.¹⁸ (one case of first stage) in 2018, Machado et al.¹⁶ in 2019 (one case full robotic) and Di Benedetto et al.¹⁷ in 2020 (two cases). Of these five case reports, the indication was colorectal liver metastases in three, intrahepatic cholangiocarcinoma in one case, and HCC in cirrhotic patients in one.

Minimally invasive surgery has shown some benefits in different areas when compared with open approach and in liver resection as well. In our experience, robotic ALPPS represents a safe and feasible procedure, preserving the same advantages of the laparoscopic and open ALPPS in experienced robotic liver centres. As a matter of fact, performing a full robotic ALPPS requires not only the completion of a complete learning and proficiency curve with the robotic platform, but also a large experience of liver surgery. Thanks to the gentle tissue manipulation, precise dissection, magnified stable view and easier vascular control, robotic approach results in reduced interstage morbidity and, therefore, lower risk of uncompleted ALPPS.^{9,15-17} Some benefits of minimally invasive approach are shared between robotic and laparoscopic approach, and further studies will clarify if technological differences will result in different clinical or intraoperative outcomes. Meanwhile, our results show that a robotic approach may represent a safe way to perform ALPPS, even in selected patients with well compensated liver cirrhosis, expanding the opportunities for these patients to get a curative surgery. ALPPS procedure is safe and feasible in patients with HCC. This is a chance for cure in unresectable patients who are selected for palliative treatment. Robotic ALPPS in cirrhotic patients with HCC deemed unresectable is an alternative when extended resection is required. This procedure has some advantages when compared with open approach. However, the procedure should be performed by experienced hepatobiliary surgeons at advanced robotic centres.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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