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ORIGINAL ARTICLE

# Transition from open to laparoscopic ALPPS for patients with very small FLR: the initial experience

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## Abstract

**Background:** Laparoscopic ALPPS (Associating Liver Partition and Portal vein ligation for Staged hepatectomy) has been reported in individual reports, but has been the authors' default option since 2015.

**Methods:** A retrospective analysis of all consecutive patients undergoing ALPPS at a single referral center was performed using a prospective database from July 2011 to June 2016. Feasibility was studied by assessing conversions. The 90-day mortality and complications were analyzed using a Dindo–Clavien score and the comprehensive complication index. Operative time, blood loss, volumetric growth, and hospital stay were examined. The CUSUM statistic was measured.

**Results:** There was no mortality and no complication grade ≥3A observed in laparoscopic ALPPS. In open ALPPS, one patient died after the procedure and 10 out of 20 patients experienced complications grade ≥3A (p = 0.006). No liver failure was observed after laparoscopic ALPPS, and two patients in the open ALPPS developed complications that precluded the second stage. The hospital stay was shorter in the laparoscopic ALPPS group.

**Conclusion:** Laparoscopic ALPPS is feasible as the default procedure for patients with very small FLR, and it is not inferior to the open approach. The use of laparoscopy in ALPPS should be encouraged to surgeons experienced with complex laparoscopy.

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## Introduction

Small liver remnant volumes are associated with significant morbidity and mortality and may have the highest impact on outcomes compared with other risk factors following liver resection.[1–3] The parenchymal sparing approach to liver resections may increase resectability and improve outcomes,[4] but there is still a group of patients who require an increase in volume and function of the planned future liver remnant to enable a potentially curative resection.[5] In these patients, morbidity and mortality may be mitigated by induction of liver regeneration prior to resection.[5] Preoperative portal vein embolization,[6–8] portal vein ligation combined with staged hepatectomy for colorectal liver metastases and most recently ALPPS (Associating Liver Partition and Portal vein ligation for Staged hepatectomy)[9,10] have all been successfully used to induce pre-resection liver hypertrophy. These have all been associated with complications[7,11,12]—particularly ALPPS, which consists of an extensive first stage procedure that includes hepatic parenchymal transection combined with portal vein ligation.

Laparoscopy reduces the surgical severity and the systemic inflammatory response for all types of elective surgery including liver resection.[13] To maintain the advantages of rapid hypertrophy associated with ALPPS, totally laparoscopic ALPPS procedures were safely performed and reported in individual patients.[14] Based on this experience, ALPPS was offered routinely as a laparoscopic procedure (lap-ALPPS) to patients with very small

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liver remnants. This analysis reports the initial experience and evaluates the feasibility of the routine use of lap-ALPPS.

## Methods

### Study design

A retrospective audit of all consecutive patients undergoing ALPPS at a single referral center for liver tumors in São Paulo, Brazil was performed. Patients undergoing ALPPS were identified in a prospective database of all liver resections since 2007, and all consecutive patients undergoing ALPPS were analyzed (Fig. 1). No patients were excluded. The primary end-point was the feasibility of lap-ALPPS and the rate of conversion to an open procedure during either stage of the procedure. Secondary end-points were complications, mortality, and volume increase.

### Setting

The first ALPPS procedure was performed in July 2011, and all patients undergoing ALPPS in the subsequent 5 years were included. All patients consented to ALPPS and inclusion into the database. The same surgeons (MAM, RCS, and FFM) performed all surgeries. In 2012, two laparoscopic ALPPS were performed in selected patients. From 2015, after completion of the 20th ALPPS procedure, laparoscopic ALPPS was offered to all patients with indication of ALPPS as the default procedure.

### Surgical technique

The first stage in both open and lap-ALPPS is the exploration of the abdominal cavity and ultrasound. In both open and lap-ALPPS, intraoperative ultrasound was performed by the senior author (MAM) who has extensive experience with this procedure. Four trocars were used in the laparoscopy. Multiple non-anatomical resections were performed on the left liver using laparoscopic or open ultrasound as guidance. A detailed description of laparoscopic liver resection is available elsewhere.[15]

In both laparoscopy and open ALPPS, the portal vein is ligated with a non-absorbable suture followed by transection. In laparoscopy, a parenchymal transection is carried from caudal to cephalad. In both techniques, the main dissection and sealing technique uses bipolar forceps supported by occasional clips. Stapler transection of larger vessels is used, and 5-0 prolene sutures are used in open surgery. The transection surface is covered with a hemostatic patch (TachoSil, Takeda, Linz, Austria) to reduce adhesion between split liver sections, and closed suction drain is left between partitioned livers in both techniques. No hilar lymphadenectomy is routinely used in either technique.

In the second stage, the right liver is fully mobilized off the retroperitoneum, diaphragm, and IVC in both ALPPS and lap-ALPPS. Stage 2 procedure is also performed laparoscopically in the lap-ALPPS group. The right Glissonian pedicle is divided with an endostapler in both techniques.[16] Staplers are then used to transect the right and—and in some patients—the middle hepatic veins followed by removal of the specimen. In lap-ALPPS, the surgical specimen is retrieved inside a large plastic bag and removed through suprapubic incision (Fig. 2). Generally the left lateral segment constitutes the future liver remnant (FLR). In some patients, the FLR may be on the right side, and in these patients the left Glissonian pedicle was divided during the second stage.[17] With few exceptions, the stage 2 was performed after waiting for three weeks to avoid problems with post-operative liver function after stage 1 by allowing maturation of the rapidly hypertrophied liver.

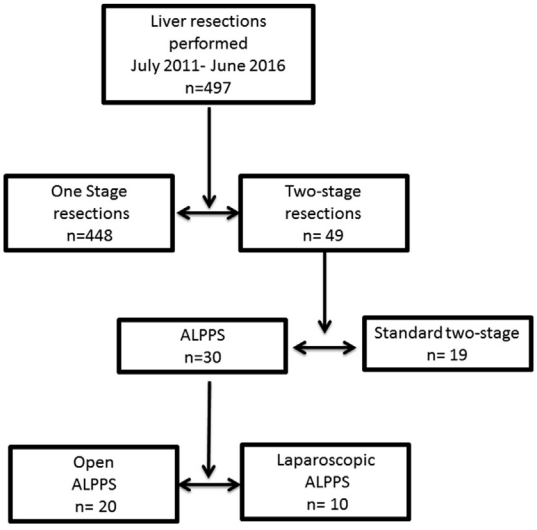


**Figure 1** The flow diagram shows all referred patients undergoing surgery for liver tumors at our institution between July 2011 and June 2016 stratified by open and laparoscopic ALPPS

### Variables

Age, gender, BMI, type of tumor, number of tumors, number of liver segments involved, standard FLR, use of neoadjuvant chemotherapy and liver histological abnormality were recorded. Surgical variables, blood loss, need for transfusion during the hospital stay, duration of operations, feasibility, FLR hypertrophy between stages, kinetic growth, and total hospital length of stay (sum of both stages) were documented. The complication severity was assessed according Dindo–Clavien classification, type by using the FABIB grading system (liver failure, ascites, bile leak, infection and post-hepatectomy bleeding),[18] liver failure by ISGLS criteria,[19] and comprehensive complication index (CCI) for quantitative analysis of complications.[20]

### Data sources and management

Complications were recorded prospectively by direct observation and entered into the database by residents and nurses under supervision of a senior fellow (TB). Additionally, hospital charts




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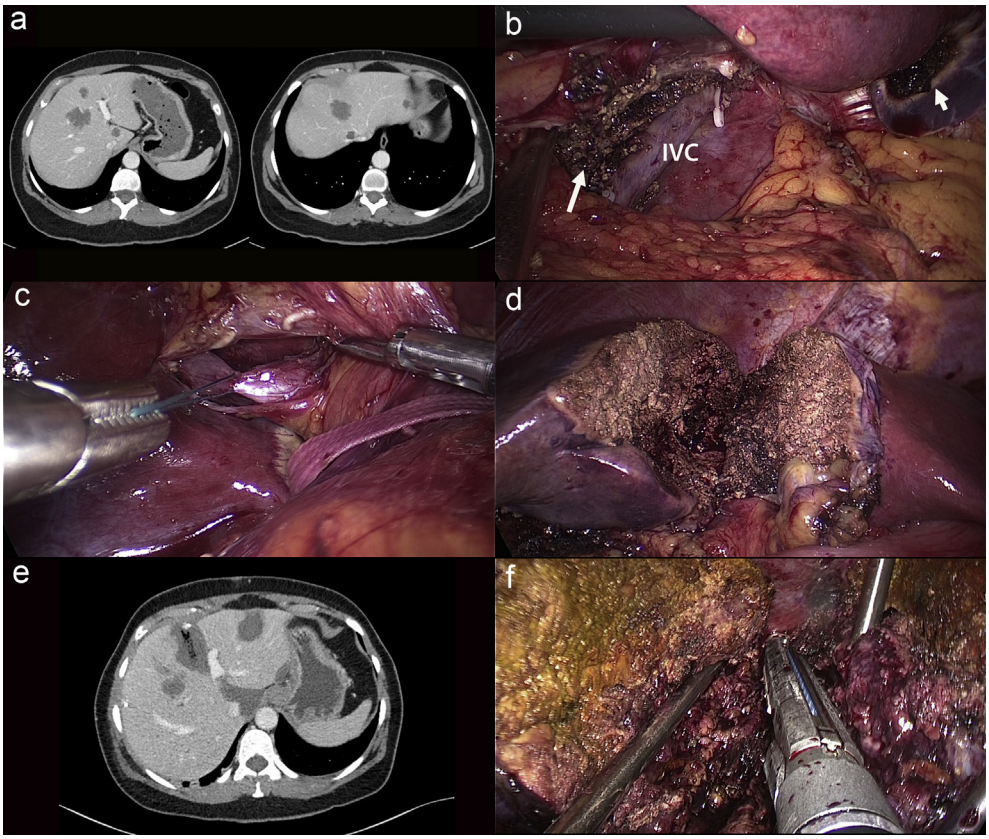


**Figure 2** Main steps for laparoscopic ALPPS. **a**. Example of a patient with bilobar disease involving the right hepatic vein, segment 4, segment 1 and two additional lesions in segment 2 and 3 resulting in a very small FLR of 0.18. ALPPS is indicated in this scenario, but it may be performed laparoscopically as shown. **b**. Intraoperative photograph of the segment 1 resection (large arrow). IVC = inferior vena cava **c**. Portal vein occlusion is performed by ligature of the contralateral portal vein without mobilization of the right lobe. **d**. The liver is transected at the level of falciform ligament. **e**. CT scan between stages shows an adequate hypertrophy of the FLR to 115%. **f**. After the right lobe is mobilized, the right pedicle and the hepatic veins are exposed, and ALPPS is completed by taking the right and middle hepatic veins using the endostapler

were reviewed retrospectively. A web-based calculator (www.assessurgery.com) was used to calculate the CCI. Operative times and transfusions given were recorded during anesthesia and entered into the prospective database in a sign-out procedure at the end of the procedure. FLR size was quantified as standardized FLR with CT or MRI volumetry and Vauthey's formula.[21] A radiologist with 10-year experience in abdominal imaging performed a volumetric analysis of all patients using the post-processing software iNtuition (TeraRecon, Houston, TX).[22] Feasibility was expressed as a proportion, hypertrophy in % of the sFLR, kinetic growth as the increase of the sFLR proportion per day, and hospital stay in days.

### Statistical analysis

Results were reported using median and range. To compare groups, the chi-squared test was used for proportions; the unpaired student-t test was used for parametric data and the Mann–Whitney U test for non-parametric data. The statistical analysis was performed using JMP version 10.0.2 for Mac (SAS, Gary, N.C., USA).

### CUSUM analysis

The result of CUSUM analysis was presented in a chart with patient numbers plotted on the x-axis and the corresponding CUSUM score on the y-axis, which allows performance over consecutive procedures to be visualized. The median CCI of the entire series was used as the control variable (x-axis). CUSUM of CCI was calculated as a cumulative sum of differences between the CCI values and the median CCI.

## Results

### Participants

Between July 2011 and June 2016, ALPPS was performed in 30 patients. ALPPS represented 69% of all two-stage hepatectomies and 6% of all liver resection performed between 2011 and 2016




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(Fig. 1). Among standard two-stage liver resections, portal vein ligation was successfully used in 13 patients and portal vein embolization (PVE) in 6 patients with no failure with these approaches. All ALPPS patients had bilobar disease. Of 28 patients who underwent the second stage, the FLR was completely cleared of tumor when at first operation. All patients underwent ALPPS due to metastatic disease (26 with CRLM, 2 with metastases from sarcoma, and 1 with metastatic GIST) except for one patient with gallbladder cancer without cholestasis. No patients with cirrhosis were included. All patients underwent preoperative chemotherapy, except two patients with metachronous disease. Demographic and operative data are shown in Table 1. No patient was found to be unresectable after exploration. In four patients, a single segment was left as the FLR (monosegment ALPPS). In four patients, the FLR was the right posterior section (reversed ALPPS).

In 10 patients, ALPPS was performed laparoscopically without conversion. Two patients refused the laparoscopic procedure due to a lack of insurance coverage. Two patients underwent reversed ALPPS and one patient a monosegment ALPPS performed laparoscopically.

Table 2 shows operative outcomes by procedure type. In open ALPPS, one patient died after the open ALPPS procedure due to post-hepatectomy liver failure and septic shock. Two patients in the open ALPPS developed liver failure after stage 1, which precluded the second stage. Table 3 shows the types of complications.

### Potential biases

There are two main potential biases in this study: selection and era bias. To address era bias, patients CCI score were plotted consecutively by time (Fig. 3a). Although complications with a CCI > 30 continued to occur throughout the series in patients undergoing open ALPPS, no patient in the laparoscopic ALPPS had CCI > 30. To use process control statistics, we also plotted a CUSUM graph for each procedure (Fig. 3b). The CUSUM graphs of the two procedures show that laparoscopic ALPPS was consistently below the median CCI of both procedures (CCI = 9). In terms of selection bias no differences in tumor burden or extent of disease were noted between the two groups (Table 1).

## Discussion

This paper reports on the feasibility of one of the most complex laparoscopic liver resections: laparoscopic ALPPS. This experience is very recent but quite promising, which warrants this report of a series of 10 patients. Extensive experience with laparoscopic liver resections[15–17,23,24] led to the conclusion that

**Table 1** Characteristics of laparoscopic *vs*. open ALPPS

| Characteristics | Open (n = 20) | Laparoscopic (n = 10) | p-Value |
|---|---|---|---|
| Age median, years (range) | 57 (28–67) | 58 (36–69) | p = 0.312 |
| Age > 60 y[a] n | 5 | 3 | p = 0.833 |
| Gender, n (f:m) | 8:12 | 6:4 | p = 0.300 |
| Total number of tumors, median (range) | 15 (8–27) | 14 (8–19) | p = 0.984 |
| Number of segments involved with tumor, median (range) | 7 (6–8) | 7 (6–8) | p = 0.271 |
| CRLM patients, n/n | 17 | 9 | p = 0.704 |
| Non-CRLM[a] patients, n/n | 3 | 1 | p = 0.704 |
| CRLM patient w/neoadjuvant chemotherapy, n/n | 16/17 | 8/9 | p = 0.634 |
| Histological abnormality,[b] n/n | 16 | 7 | p = 0.541 |
| Patient requiring RBC transfusion,[a] n/n[c] | 7 | 2 | p = 0.398 |
| **Blood loss stage 1, ml median (range)** | **420 (280–1400)** | **200 (110–300)** | **p < 0.001** |
| **Blood loss stage 2, ml median (range)[d]** | **460 (240–1200)** | **320 (150–800)** | **p = 0.010** |
| Operative time stage 1, min, median (range) | 300 (200–490) | 300 (208–340) | p = 0.405 |
| Operative time stage 2, min, median (range)[d] | 190 (60–380) | 180 (140–300) | p = 0.485 |
| Operation duration >300 min stage 1,[a] n/n | 10 | 4 | p = 0.604 |
| Extended resections *vs*. Hemihep., n:n | 13:5[d] | 7:3 | p = 0.900 |
| sFLR prior to stage 1, proportion median (range) | 0.16 (0.08–0.24) | 0.19 (0.13–0.30) | p = 0.139 |
| sFLR prior to stage 2, proportion median (range)[d] | 0.37 (0.24–0.61) | 0.39 (0.29–0.51) | p = 0.351 |
| Time between stages, days median (range)[d] | 21 (11–38) | 21 (9–30) | p = 0.256 |

Lines with statistical differences were marked as bold.
RBC, red blood cell.
[a] Known risk factors for poor outcomes after ALPPS (reference 25).
[b] Histological abnormality: fibrosis, steatosis >30%, sinusoidal obstruction syndrome, chemotherapy-associated steatohepatitis.
[c] At any time during hospital stay.
[d] 2 patients, who did not complete the 2nd stage have no data in this category.

**Table 2** Outcomes of laparoscopic *vs*. open ALPPS

| Characteristics | Open (n = 20) | Laparoscopic (n = 10) | p-Value |
|---|---|---|---|
| Feasibility, n | 18 | 10 | p = 0.287 |
| sFLR hypertrophy*, %, median (range) | 152 (56–215) | 118 (42–157) | p = 0.072 |
| Kinetic growth of sFLR, proportion per day, median (range) | 0.02 (0.006–0.078) | 0.012 (0.05–0.045) | p = 0.281 |
| Mortality, n (%) | 1 | 0 | p = 0.472 |
| **Complications > IIIA (severe) in both stages, n (%)** | **10** | **0** | **p = 0.006** |
| **Comprehensive complication index (CCI) in both stages, median, (range)** | **21 (0–100)** | **4 (0–20.9)** | **p = 0.002** |
| **Liver failure by ISGLS criteria in both stages, n (%)** | **8** | **0** | **p = 0.019** |
| **Total hospital stay* median, days (range)** | **14 (10–31)** | **11 (8–20)** | **p = 0.004** |

Lines with statistical differences were marked as bold.
sFLR, standardized future liver remnant; Complications > IIIA according to the Dindo–Clavien score; CCI, comprehensive complications index (reference 20); ISGLS, International Study Group for Liver Surgery (reference 19). * 2 patients, who did not complete the 2nd stage, were excluded from this analysis.

**Table 3** Complications of laparoscopic *vs*. open ALPPS

| Type of complications[a] | Open (n = 20) | Laparoscopic (n = 10) | p-Value |
|---|---|---|---|
| **Post hepatectomy liver failure, n/total** | **8** | **0** | **p = 0.019** |
| Post hepatectomy ascites, n/total | 5 | 1 | p = 0.333 |
| Post hepatectomy bile leakage, n/total | 6 | 2 | p = 0.559 |
| **Post hepatectomy infection, n/total** | **11** | **1** | **p = 0.017** |
| Post hepatectomy bleeding, n/total | 5 | 1 | p = 0.333 |

Lines with statistical differences were marked as bold.
[a] FABIB grading system (reference 18).

laparoscopy may reduce operative severity and complications associated with open abdominal surgery such as blood loss, which is a known risk factors for inferior outcomes in open ALPPS.[25] Despite a certain hesitancy to broaden the indications for major laparoscopic liver resections,[26] major laparoscopic hepatectomies are common in many experienced centers, e.g. as donor hepatectomies in transplantation.[27–29] While ALPPS has high complication rate,[12,30] lap-ALPPS may achieve a lower postoperative mortality and lower morbidity.

According to the Balliol classification, the current report may be considered a 2a development study to establish technical safety and procedural success. Laparoscopic ALPPS should be explored further, possibly in a prospective comparative study among centers experienced with the highest complexity of laparoscopic liver resections. Similar to other ALPPS modifications,[31,32] laparoscopy reduces the extent of surgery during stage one. Better visualization of the transection area and minimized biliary injuries recommends lap-ALPPS for general use by experienced surgeons. In contrast to the open procedure, the identification of lesions cannot depend on palpation—the presence of lesions must be clearly mapped out by cross-sectional imaging prior to the procedure with confirmation via laparoscopic intraoperative ultrasound. The lower regenerative response compared to open ALPPS, while interesting in the context of rapid hypertrophy mechanism, may not be clinically relevant. Reports about partial transection in open ALPPS have shown reduced hypertrophy rates as well.[32]

The Zurich group has recently proposed "partial ALPPS" to improve the safety of the procedure.[32] Their rationale is to only perform a part of the parenchymal transection in the first stage, but to use the open approach. Similarly, the first international meeting on ALPPS concluded that a change in the way in which ALPPS is performed may result in better results.[33,34] The main message was to keep the first step small, reduce liver partition, avoid liver mobilization and postpone the second step until recovery of liver function. While reducing the depth of the parenchymal transection may reduce the invasiveness of the procedure, data from the current study also suggest advantages of the laparoscopic approach.

The observation that lap-ALPPS has fewer complications and results in a shorter hospital stay are based on relatively few patients and has yet to be confirmed in a larger series. Also, it is important to stress that laparoscopic ALPPS should be performed by surgeons with great experience in both ALPPS and laparoscopic liver resection. It is also too early to speculate about the oncological value of lap-ALPPS. However, it has repeatedly been demonstrated that there is no evidence to assume that laparoscopy reduces the radicality of tumor resection.[24,26,35,36]

The main limitation of this study is its observational study design with respective biases in selection and era. A patient match analysis or propensity scoring was not performed because of the limited number of patients. Selection bias can only be reliably eliminated by randomization. Randomization is difficult for this rare operation. Only 6% of all liver resections performed by this center required ALPPS over the last 5 years.

In conclusion, the current study demonstrates that the laparoscopic approach is feasible in ALPPS and does not appear inferior to the open approach. While indications for ALPPS are rare, the authors encourage the use of laparoscopy in ALPPS and




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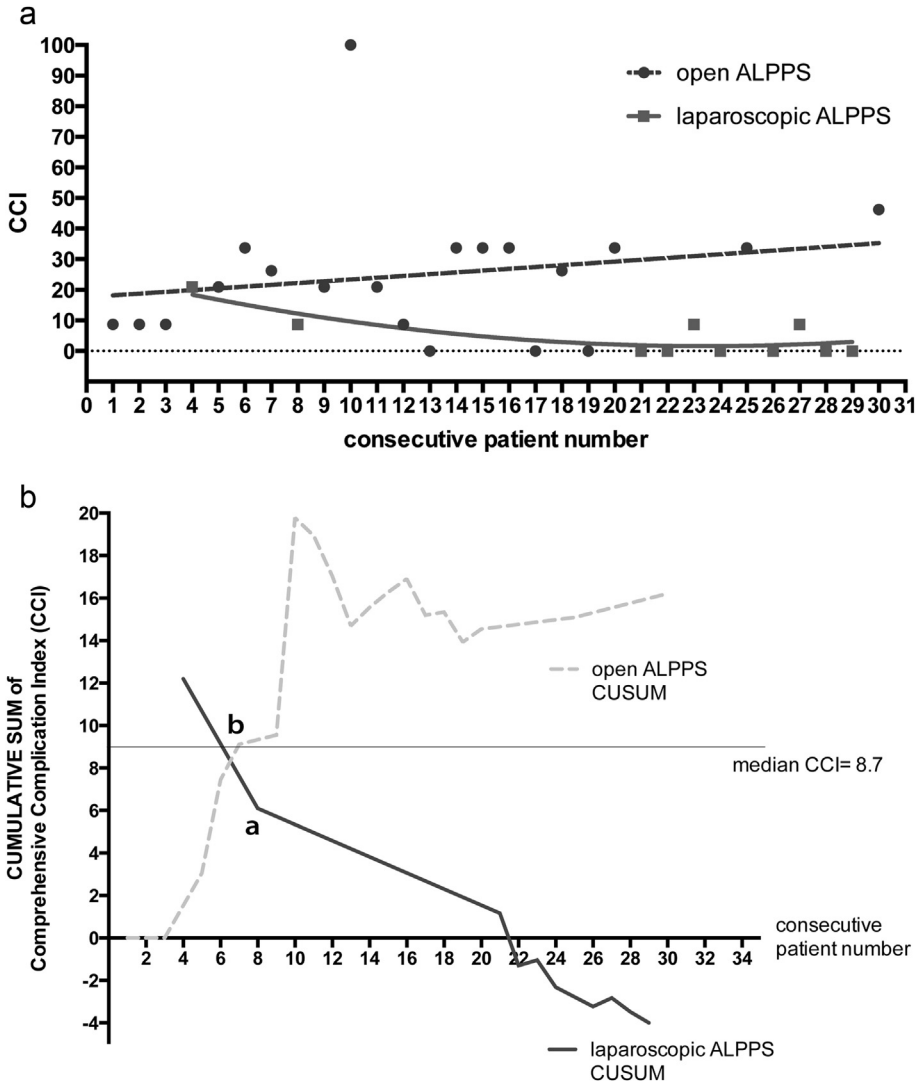


**Figure 3** CCI comparison between open and lap-ALPPS. **a**. Comprehensive complication index (CCI) for consecutive patients undergoing ALPPS. The CCI allows a visual depiction of complications in the course of consecutive laparoscopic and open ALPPS procedures using a second-degree polynomial regression function. **b**. CUSUM (cumulative sum) chart of open and laparoscopic ALPPS using the median CCI of the entire series (CCI = 9) as the control variable (=x axis). Laparoscopic ALPPS remains below the median CCI after the first 2 patients (point a). Open ALPPS remains above the median CCI after the first 6 patients (point b)

support a prospective evaluation by surgeons experienced with complex laparoscopic liver surgery.

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Drs. Machado, Makdissi, Surjan, Bassères and Schadde have no conflicts of interest or financial ties to disclose.

**Conflicts of interest**

None declared.

**Author's contribution**

All authors equally contributed to acquisition of data, and/or analysis and interpretation of data.

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