

ALPPS PROCEDURE FOR THE TREATMENT OF BILOBAR MULTIPLE LIVER METASTASIS FROM COLORECTAL CANCER: FIRST CASE IN RN MACEDONIA

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ABSTRACT

Introduction: ALPPS (Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy), is a recently developed procedure, first performed by HJ Schlitt in Regensburg, Germany. The technique developed two stages of hepatectomy. The ALPPS procedure has been introduced to increase the volume of future liver remnant, much more than the other technique, such as PVE (portal vein embolization).

The first ALPPS in our country was introduced and performed by our team on May 15th, 2018.

Results: The 60-year-old patient was previously operated on for rectal cancer in 2017 at another institution. The operation was performed with anterior resection and the patient was in long term adjuvant chemotherapy. One year after surgery, the patient has multiple bilobar liver metastases and increased tumor markers that led to instant admission to our institution for liver resection. In the first stage, we performed four metastasectomies on the left lobe with right portal vein ligation and transection on the Cantlie line. The second stage was performed after a CT evaluation on the eighth day, with significant hypertrophy on the left lobe. Pathological findings reported ten metastases on the right lobe with a diameter 1-3 cm. The patient was on the long-term chemotherapy, and after one year he had other MS in the IVa segment of the liver. We also performed a metastasectomy. The patient died 32 months after ALPPS.

Conclusion: ALPPS is a safe and feasible procedure for the treatment of bilobar liver metastasis from colorectal cancer. It could provide long-term survival for patients.

Keywords: ALPPS, metastasis, portal vein ligation, two stage, hepatectomy.

INTRODUCTION

Colorectal cancer (CRC) is a common malignancy of the digestive system, the second most common in women, the third in men [1].

CRC is the fourth deadliest cancer worldwide, with nearly 900,000 deaths annually [2].

In approximately 15% to 25% of patients, liver metastases (CRLM) are simultaneously present at initial diagnosis [3]. Hepatic resection is the only potentially curative treatment for patients with liver metastases [4]. Liver tumors that are extensive, multifocal, or critically located often require advanced liver resection techniques, thus allowing liver resection in such cases [5].

Primarily due to insufficient future liver volume (FLR) leading to posthepatectomy liver failure (PHLF), 20% of these patients are eligible for liver resection [6].

PHLF is the weakening of one or more functions. These include hyperbilirubinemia, hypoalbuminemia, prolonged prothrombin time (PT), elevated serum lactate, and varying degrees of hepatic encephalopathy and/or ascites during the postoperative period.

PHLF is closely related to the volume and function of the remaining liver, and these two variables are the main determinants of the adequacy of FLR, and for this reason their assessment is necessary before massive hepatectomy [7].

In order to increase the resectability rate, several approaches have been proposed, such as portal vein embolization [8] and the so-called two-stage liver resection [9], whereby resection of colorectal liver metastases (CRLM) in one hemi-liver was followed by a second stage resection of CRLM in the contralateral lobe, thereby allowing time for hypertrophy of the FLR between the two procedures.

Portal vein occlusion and two-stage liver resection unfortunately face a lack of compensatory hypertrophy or even the risk of tumor progression in the time interval required before resection (2-3 months).

Surgical portal vein ligation (PVL) and portal vein embolization (PVE) require 4-8 weeks of waiting time and re-evaluation before the tumor can be safely resected [10].

The waiting time between two-stage hepatectomy (TSH), with or without interstage chemotherapy, is 8-12 weeks [11].

To promote FLR hyperplasia and shorten the interval, a new 2-stage hepatectomy named Associating Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS) has been developed [12].

ALPPS induces FLR hypertrophy up to 80% in less time than portal vein embolization (PVE)

or portal vein ligation (PVL) and 2-staged liver resection [13].

In 2007, Dr. Hans Schlitt in Regensburg, Germany first performed ALPPS on a 49-year-old patient with asymptomatic jaundice from a suspected perihilar cholangiocarcinoma, which he called liver bipartition. In 2008 Dr. Schlitt was the first to perform an associated partition to the liver and ligature to the portal vein for two-stage hepatectomy (ALPPS) for colorectal hepatic metastases of CRLM.

Although unpublished and only informally communicated by the author to some of his colleagues, the new technique was quickly adopted and applied by a large number of surgeons in Germany [14].

The first formal report of this new approach was in April 2011 by Hauke Lang at a poster presentation of 3 case series during the ninth E-AHPBA meeting in Cape Town, South Africa [15].

After the publication of 25 such cases from 5 German centers in the *Annals of Surgery* in March 2012, a new liver regeneration method named by Clavien as "Association of Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS)" became known worldwide. [16].

In the first stage of ALPPS, the right portal branch is ligated, and the liver is divided at the site of the falciform ligament, whereby, unlike classical hepatectomy, the tumor hemiliver is left in situ and remains vascularized only by the right hepatic artery. The biliary and systemic venous drainages represented by the right biliary duct and corresponding hepatic veins are preserved. In the second stage, which is performed within 7 to 15 days after the first stage, the tumor hemiliver is removed by cutting the right hepatic artery, the biliary duct, and the systemic venous pedicle [3].

In order to provide a similar hypertrophic profile as standard ALPPS, but probably with lower complications and mortality, several modifications of the ALPPS procedure have been introduced [17].

Partial ALPPS was described by Alvarez et al. and consists of dividing the portal vein of the diseased half-liver to the middle hepatic vein [18].

The so-called "mini-ALPPS" combines partial parenchymal transection and intraoperative PVE without dissection of the porta hepatis [19].

Robles et al. replaced transection during the first stage by applying a tourniquet around a

1 cm parenchymal groove in the future transection line to ensure parenchymal compression and intrahepatic collateral occlusion along the future transection line (Tourniquet ALPPS) [20].

Jiao et al. used radio frequency to create a virtual liver partition, combined with portal vein ligation. The RFA produce a precise avascular area up to 1 cm wide [21].

Similar to RFA, Cillo et al. used microwave ablation on segment IV in the first stage operation to complete the liver partition [22]. In recent years, there have been reports of ALPPS performed successfully and safely by totally laparoscopic [23] and robotic assisted approaches [24]. The purpose of this study is to describe our initial experience using the ALPPS method, applied on May 15, 2018, at our clinic. This is, to our knowledge, the first case in which this method has been applied in our country.

This study also serves to compare our experience from this case with the results of other authors.

CASE REPORT

The 60-year-old patient was previously operated on for rectal cancer in 2017 at another institution. The operation was performed with anterior resection, and the patient was in long term chemotherapy afterwards. One year after CT evaluation and PET-scans, the patient showed multiple bilobar liver metastases and increased tumor markers. After a thorough review by the multidisciplinary team, it was decided to proceed to the ALPPS procedure as a feasible means to perform extensive or bilobar liver resections, we expected to provide a better outcome for our patients.

The procedure was performed in two steps. The first stage consisted of exploratory laparotomy, assessment of resectability with intraoperative ultrasound and positioning, the team

performed four metastasectomy on the left lobe with right portal vein ligation and transection in the Cantlie line.

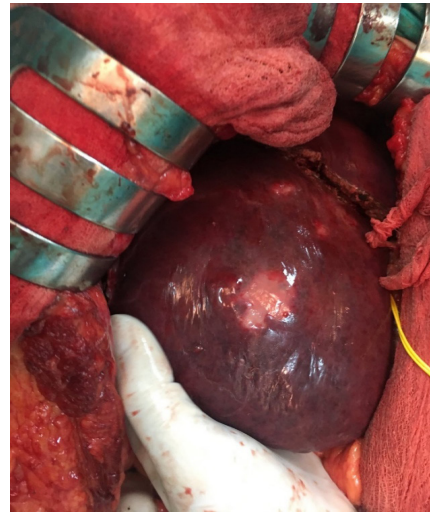


Fig. 1. Liver metastases in right hepatic lobes



Fig. 2. Intraoperative ultrasound

The right liver lobe was completely mobilized from the cava vein after in situ splitting, the right extended lobe is covered in a plastic bag to prevent adhesions, and the abdomen is drained and closed. The operating time was 300 minutes.

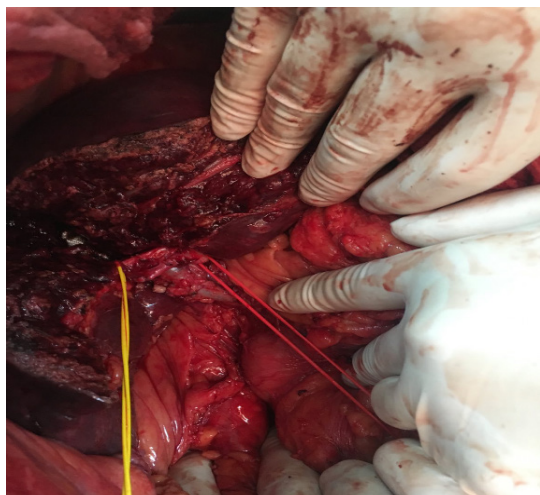


Fig. 3. *Vessel loops in the dissected portal triad*

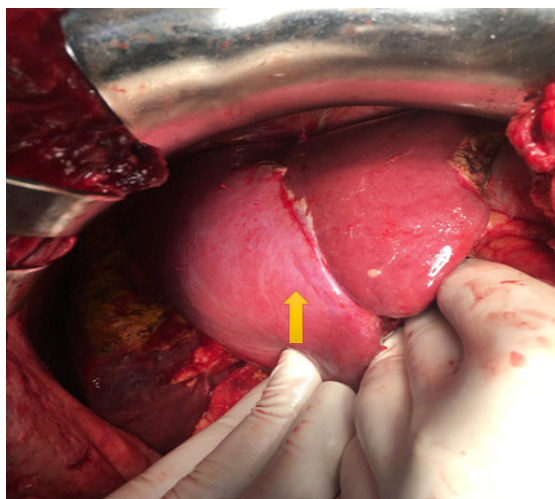


Fig. 4. A – *On day eight, with significant hypertrophy on the left lobe (arrow shows right lobe)*

The patient was under intensive care, had normal liver function and the first step was performed without complications. The patient stayed in the intensive care unit overnight.

The second stage was performed after a CT evaluation on the eighth day. There was significant hypertrophy on the left lobe. Pathological findings reported ten metastases on the right lobe with diameters of 1-3cm.

The second step of the procedure was completed by re-laparotomy. After careful adhesiolysis, the right hepatic artery, right hepatic duct, and the right hepatic vein were ligated. The liver resection was completed. Finally, a drain was placed at

the resection surface and the abdomen was closed. The operating time was 260 minutes. The patient was in the intensive care. Blood transfusion was not required. The vital parameters were normal. The liver function was normal by post-operative days, and the patient was discharged after 23 days, without complications.

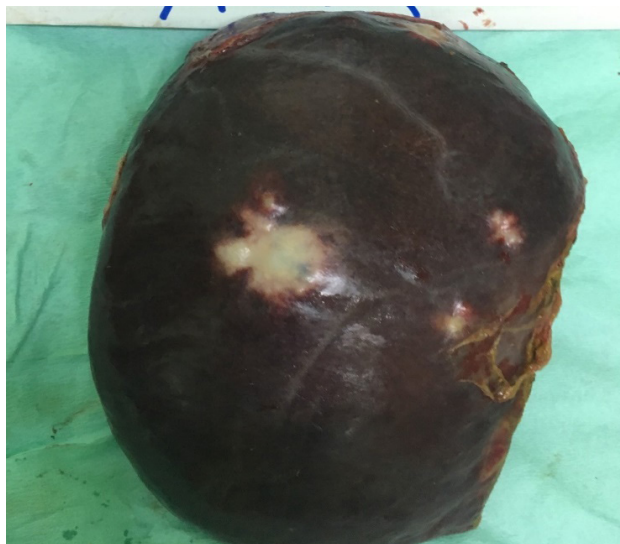


Fig. 5. A – *Transection of the right lobe*



Fig. 5. B – *Multiple liver metastases*

The patient was on long-term chemotherapy. After one year, in control review of CT evaluation and tumor markers, he had other MS in segment IVa. In our institution, we also performed a metastasectomy.

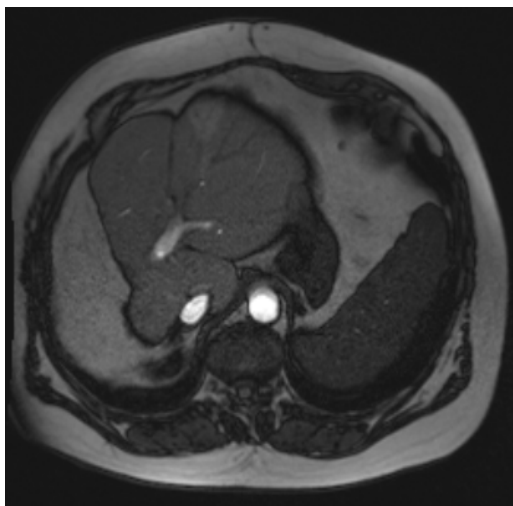


Fig. 6. A – Major liver tumor localized in segment IV

After discharge, the patient was referred to medical oncologists for control which included abdominal ultrasounds, abdominal CT-scans or MRI at 3, 6 and 12 months after surgery.

Serum tumor markers were assessed at 3, 6, and 12 months after surgery.

He had long term chemotherapy. Patient died 32 months after ALPPS at the age of 63.

DISCUSSION

The only chance to obtain long-term survival in patients with hepatic tumor or metastasis from other primary cancers is complete tumor resection of the liver.

The median survival time for untreated patients is less than 6.9 months [25].

The ALPPS procedure should be considered as an alternative surgery in patients with liver tumors that do not have enough remnant liver tissue after surgery, with the principal aim to avoid postoperative liver failure, as well as to achieve R0 resections, with positive oncologic outcomes.

To perform the ALPPS procedure, precise anatomical knowledge is of crucial importance.

Injury to tumor-bearing branches of the hepatic artery of the liver (future specimen) may cause necrosis and procedure failure.

In addition, injury to the biliary structures and bile leakage during the interstitial phase must be avoided.

The ALPPS concept is based on a complete portal vein devascularization of the tumor-bearing liver with preservation of arterial blood flow, thus causing massive hypertrophy of the contralateral part of the liver.

In order to achieve a more systematic follow-up and review of the ALPPS procedure, De Santibanes, Lang and Clavien introduced an international internet-based case registry based at the Department of Surgery at the University Hospital of Zurich, Switzerland in 2012.

ALPPS can predictably induce an accelerated FLR growth of 40%-160% in 6–9 days, a short period in which major tumor progression is unlikely and R0 resection can be performed without troublesome adhesions, thus broadening the indications for curative resection without risk of PHLF [26].

According to Liu et al. ALPPS, when compared with portal vein embolization (PVE) and two-stage hepatectomy (TSH), was associated with a greater increase in future liver remnant (FLR) and more frequent completion of stage 2 resection, but with a higher morbidity and mortality rates in ALPPS patients than those with PVE and TSH [27].

The Scandinavian multicenter randomized controlled trial (LIGRO trial) of 97 subjects with colorectal liver metastasis (CRLM) compared ALPPS with TSH in terms of percentages of patients who completed both stages of treatment - resection rates (primary outcome), complications, radicality and 90-day mortality measured by final intervention (secondary outcomes).

In the ALPPS group, compared to the TSH group, the resection rate (RR) was (92% vs 57%); there were no differences in complications (43% vs 43%); 90-day mortality was (8.3% vs 6.1%); R0 RRs (77% vs 57%) respectively [28].

Joechle et al. found no difference in proliferation, apoptosis, and vascularization in CRLM when comparing matched patients who underwent ALPPS with those who underwent standard (one-step) liver resection, further supporting the use of ALPPS in selected patients with otherwise non-resection CRLM [29].

There are still different views on the benefit of partial partition of the liver parenchyma (p-ALPPS) compared to complete partition of the liver and ligation of the portal vein for staged hepatectomy (ALPPS) for reducing morbidity and mortality rates.

According to Huang et al. p-ALPPS is safer than ALPPS in terms of morbidity and mortality with the same rate of FLR hypertrophy in patients without cirrhosis, while ALPPS appears to have a better outcome in the cirrhosis group [30].

Chan et al. found no significant difference in operative time and blood loss for stage I and II between complete ALPPS and partial ALPPS in a study of 25 patients with hepatocellular carcinoma. In stage II, all patients were operated on without any complications between the stages. Herein, ALPPS induced faster hypertrophy of the future liver remnant than p-ALPPS [31].

Further studies are needed to examine patient selection and outcomes of the two procedures [32].

There is a discrepancy between the volume and functional growth of the liver, with the increase in function according to experience, so far, being about 50% compared to the increase in volume.

The pathophysiology of PHLF is essentially based on disruption of normal hepatocyte regeneration and impaired liver homeostasis.

Despite efforts to better select candidates, the incidence of post-hepatectomy liver failure (PHLF) after ALPPS still ranges between 7 and 30%, representing a major cause of 90-day mortality [33].

In the study by Schadde et al., which included 320 subjects from the International Registry of patients undergoing ALPPS from April 2011 to July 2014, the overall 90-day mortality was 8.8%, and the main cause was postoperative liver failure in 75% of patients [34].

Rapid identification of preoperative predictors of PHLF in the form of biochemical parameters and imaging features are of paramount importance for every liver surgeon and form the cornerstone of his management [35].

The predictive risk factors of PHLF can be categorized into the following: patient related, liver related, and surgery related.

Age, insulin depletion, sepsis, hyperbilirubinemia, renal insufficiency, cardiopulmonary compromise and thrombocytopenia, liver cirrhosis, cholestasis, and intraoperative hemorrhage are major factors for the development of postoperative morbidity [35, 36].

According to the International Study Group for Liver Surgery (ISGLS) criteria, fourteen per-

cent of patients developed liver failure after stage 1 ALPPS.

ISGLS criteria are positive when the INR value is 1.3 and the bilirubin value is more than 20 micromol/L (1.2 mg/dL).

These patients and patients with a Model of End-Stage Liver Disease (MELD) score greater than 10 before stage 2 were at significantly higher risk for 90-day mortality after stage-2 [34].

Scintigraphic liver function tests, such as hepatobiliary scintigraphy (HBS) using (99m) Tc-mebrofenin-hepatobiliary-scintigraphy (HBS) in combination with single-photon emission computed tomography, provide quantitative information on segmental liver function, and thereby for the function of FLR. The FLR penetration rate for safer liver resection has been calculated to be 2.7/min/m², or higher in surgical patients with and without compromised liver parenchyma [37,38]. Accurate patient selection is one of the most important factors in minimizing morbidity and mortality associated with ALPPS procedure.

Independent factors for severe ALPPS-related complications were red blood cell transfusion, ALPPS stage 1 operative time greater than 300 minutes, patients older than 60 years, and non-CRLM [39]. Patients undergoing ALPPS who are younger than 60 years and those with liver metastases due to colorectal cancer (CRLM) and hepatocellular carcinoma have lower rates of morbidity and mortality than patients with gallbladder cancer or cholangiocarcinoma undergoing ALPPS, whose prognosis is worse [40].

Colorectal liver metastases (CRLM) are considered the most common indication for ALPPS procedure, although, there could be an appropriate surgical approach in other cases of primary liver tumors, such as hepatocellular carcinoma and cholangiocarcinoma.

In a study of 437 patients from 16 centers, Linecker et al. observed a change in indications towards colorectal liver metastases from 53% to 77% and a reverse trend in biliary tumors from 24% to 9% [41].

Recent studies have shown a stimulating effect of ALPPS on cell proliferation, which implies that ALPPS not only increases liver volume, but also improves the function of the future remnant.

To minimize PHLF, 20 to 25% of liver is needed in healthy livers while 30 to 35% in diseased livers [42].

Rapid FLR hypertrophy induced by the first stage of in situ split hepatectomy results from both portal diversion and parenchymal transection in ALPPS. This allows the liver to be resected within a few days during the same hospital stay, minimizing the consequences associated with the development of adhesions.

Some authors initially suggested placing a plastic sheet at the site of liver division in order to minimize adhesions, today most surgeons prefer a hemostatic sheet. We used a sterile plastic bag for that purpose.

Wrapping the whole right lobe is not recommended because of the possible undrained fluid collections within the bag. Bioactive sealants have been applied to the cut surface to prevent adhesions, with the advantage that they do not have to be removed.

ALPPS produces good oncological outcomes in terms of disease-free survival time (DFS) and overall survival (OS), with acceptable morbidity and mortality rates.

The 5-year survival rate after R0 resection of liver metastases is approximately 50%. More than half of the patients develop a recurrence within 2 years. Patients who undergo reoperation for recurrent metastases have similar recurrence-free survival (RFS) times [4].

The average time between the first and second step of the procedure was 10.8 ± 2.9 days. The average hospital stay was 24.1 ± 13.3 days [43].

According to the results of Alvarez et al. in a prospective study of 30 patients, the average hospital stay was 16 days. Overall survival and disease-free survival at 1 year were 78% and 67%, and at 2 years were 63% and 40%, respectively [18].

In the systematic review by Baili et al., after a median follow-up of 7 months (range 3–60), the recurrence rate was 18.9%. Disease-free survival ranged from 3 to 60 months with a median of 10 months and overall survival ranged from 3 to 60 months with a median of 11 months [44].

In this case, the operative time in the first stage was 300 minutes, and in the second stage it was 260 minutes, without the need for blood transfusion. The patient was discharged from the hospital after 23 days. After one year, the patient recurred metastasis in the IVa segment, for which a metastasectomy was performed. The patient died 32 months after ALPPS at the age of 63 years.

Further advances in patient selection, surgical techniques and perioperative management are required to minimize rates of complications [44].

CONCLUSION

ALPPS offers a feasible, but surgically demanding, liver-first approach for the treatment of otherwise unresectable bilobar liver metastases from colorectal cancer.

In terms of disease-free survival time and overall survival, ALPPS provides good oncological outcomes.

The correct selection of patients and a multidisciplinary approach in preoperative and postoperative treatment are necessary to achieve good postoperative results.

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Резиме

ALPPS КАКО ПРОЦЕДУРА ЗА ЛЕКУВАЊЕ БИЛОБАРНИ МЕТАСТАЗИ НА ЦРНИОТ ДРОБ ОД КОЛОРЕКТАЛЕН КАРЦИНОМ: ПРВ СЛУЧАЈ ВО РС МАКЕДОНИЈА

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Вовед: ALPPS (Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy) е неодамна развиена процедура, првпат изведена од HJ Schlitt во Регенсбург, Германија. Техниката разви две фази на хепатектомија. Процедурата ALPPS е воведена за да се зголеми обемот на идниот црн дроб, многу повеќе од другата техника, како што е PVE (емболизација на порталната вена).

Првиот ALPPS во нашата земја беше претставен и изведен од нашиот тим на 15 мај 2018 година.

Резултати: Пациент на возраст од 60 години, претходно опериран поради ректален карцином во 2017 година, во друга институција. Направена предна ректална ресекција, постоперативно пациентот на долг циклус на хемотерапија. По една година, со наод на повеќе билобарни метастази во црниот дроб и зголемени туморски маркери, примен е во нашата установа за ресекција на црниот дроб. Во првата фаза извршивме четири метастазектомии на левиот лобус со лигатура на десната портална вена и трансекција по Cantlie-ова линија. Втората фаза беше изведена по осмиот ден, по КТ-евалуација, при што се гледа значителна хипертрофија на левиот лобус. Патолошкиот наод е со десет метастази на десниот лобус со дијаметар од 1 до 3 cm. Пациентот постоперативно на хемотерапија, по една година со друга MC промена во сегментот IVA. Се направи метастазектомија. Пациентот почина по 32 месеци по ALPPS.

Заклучок: ALPPS е безбедна и изводлива процедура за третман на билобарна метастаза на црниот дроб од колоректален карцином. Се очекува да обезбеди долгорочно преживување за пациентите.

Клучни зборови: ALPPS, метастази, лигација на вена порта, два стадиуми, хепатектомија