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SUCCESSFUL TWO-STAGE TRANSPLANT HEPATECTOMY USING THE ALPPS PROCEDURE FOR ADVANCED HEPATOCELLULAR CANCER

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In the presented case, after liver transplantation (LT) for hepatocellular cancer (HCC), the disease progressed in the graft, left lung and bronchopulmonary lymph nodes after 16 months, according to the Milan criteria. Against the background of combined treatment – hepatic artery chemoembolization (HAC), systemic targeted therapy and stereotactic radiotherapy for metastatic node of the left lung – HCC in the extrahepatic foci was stabilized. In this situation, we considered resection of the liver transplant as the only therapeutic option that provides a chance for significant prolongation of the patient's life. However, extensive resection of the right liver lobe seemed unsafe due to a number of limiting factors – borderline functional residual capacity of the remaining liver: future liver remnant (FLR), 599 cm^3 (32%); plasma disappearance rate (PDR), 12.3%/min; tumor invasion of the middle hepatic vein basin. In this case, right portal vein branch (RPVB) embolization could promote vicarious hypertrophy of the remaining part of the liver, but the waiting period usually exceeds three to four weeks, and the RPVB was already partially blocked by the tumor at that time. The only option for surgical intervention was, in our opinion, two-stage hepatectomy according to the Associated Liver Partition and Portal Vein Ligation for Staged hepatectomy (ALPPS) procedure, despite the absence of literature data on the performance of such operations on a liver transplant. On postoperative day 5 from the first stage, a 799 cm^3 FLR hypertrophy was achieved, which allowed to perform the second stage of intervention relatively safely. Competent tactics regarding medication in the intensive care unit (ICU) and renal replacement therapy allowed to cope with sepsis and acute renal failure – the prevailing postoperative complications.

Keywords: hepatocellular cancer, liver transplantation, Milan criteria, transplant hepatectomy, Associated Liver Partition and Portal Vein Ligation for Staged hepatectomy (ALPPS).

INTRODUCTION

Currently, LT is the most effective treatment for HCC patients on the background of liver cirrhosis. Strict selection of recipients according to modern criteria allows achieving acceptable outcomes. Commonly known and most widespread in clinical practice, the Milan criteria, demonstrate a 5-year overall survival of about 70–80% according to different sources [1, 2]. Available literature data shows that the indications for LT in HCC can be expanded. The use of the California and "up to seven" criteria slightly worsens the long-term outcomes: overall survival 75% and 71%, respectively [2]. Despite satisfactory survival rates, tumor aggressiveness and postoperative immunosuppression lead to recurrence of the disease in 15–20% of cases within two years [3]. In the current realities, there is a wide arsenal of treatment options for relapse in the form of systemic antitumor targeting therapies, locoregional therapy methods: hepatic arterial chemoembolization (HAC), radiofrequency ablation (RFA) and transplant hepatectomy. According to several available reports, active radical surgical tactics, if technically feasible, demonstrate the best survival rates after recurrence. Inability to perform hepatectomy has been shown to be an independent predictor of poor prognosis [4]. Median survival after tumor recurrence is 65 months in patients with HCC amenable to surgery, compared to 5 months in patients not suitable for surgery [5]. In a single-center retrospective study evaluating 106 patients developing posttransplant HCC recurrence, it was demonstrated that patients receiving surgical therapy had significantly longer survival (27.8 months) than those receiving nonsurgical therapy (3.7 months) [6]. Available data on transplant hepatectomy are extremely scarce (less than 2000 operations) due to the objective complexity of technical execution and the risks of developing post-resection liver failure. Operation – two-stage hepatectomy – ALPPS is a variant of aggressive approach in case of insufficient liver reserve. In the sources we studied, the most common extent of graft resection was bisegmentectomy. Extensive hepatectomies were rarely performed. There were no mentions in the literature about two-stage hepatectomy according to the ALPPS technique in patients with recurrent HCC in the graft.

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DESCRIPTION OF CASE

Male patient, 45 years old, diagnosed with HCC, T2N0M0 stage II. G3. BCLC A. on the background of Child–Pugh B cirrhosis, MELD 23. Chronic hepatitis C since 2014 (Complete eradication after antiviral therapy in 2015). Chronic hepatitis B.

According to abdominal contrast-enhanced computed tomography (CT) scan carried out on June 10, 2019: HCC nodule in the 7th segment of the liver 25 × 21 mm, cirrhosis. Alpha-fetoprotein (AFP) level as of June 15, 2019, was 3.5 IU/mL. In July 2019, he was put on the waiting list for orthotopic LT at Russian Research Center of Radiology and Surgical Technologies in St. Petersburg. In neoadjuvant mode, HAC was performed on July 23, 2019. According to the control abdominal CT scan on April 23, 2020 (9 months after HAC): complete response according to mRECIST. The HCC node completely contains embolisate, is avascular, measuring 18 × 14 mm. Abdominal CT scan on September 09, 2020 (14 months after HAC): progression of disease (PD) according to mRECIST. HCC node is vascularized and has dynamically increased in size – 41 × 31 mm. An increase in AFP over time was also noted – September 09, 2020 – 35 IU/mL. The patient underwent another HAC on September 30, 2020.

Subsequently, LT from a deceased donor was performed using the piggy-back technique on October 01, 2020. The waiting list period was 13 months. At the time of LT, the tumor process in the liver was within the Milan criteria. In the early postoperative period, on October 7, 2020, mechanical splenic artery embolization was performed to correct the splenic artery steal syndrome. In the postoperative period, the patient received a standard triple-drug immunosuppression treatment consisting of tacrolimus, mycophenolic acid, prednisolone. At the outpatient stage of treatment, immunosuppression was corrected: everolimus, tacrolimus. The underlying disease progressed 16 months after LT. A CT scan conducted on February 01, 2022 revealed a 52 × 48 mm HCC node in the 8th segment of the liver, the para-aortic and bronchopulmonary lymph nodes were enlarged, and there was a metastatic focus in the third segment of the left lung 17 mm. The focus in the lung was histologically verified. Lenvatinib therapy was administered from March 2022. In September 2022, according to CT scan, the foci continued to grow in the graft, left lung, and lymph nodes. In September 2022, HAC was performed and a complete response to treatment was achieved according to mRECIST criteria. In February 2023, stereotactic radiation therapy was performed on the metastasis area in the left lung and bronchopulmonary lymph nodes on the left side. Stabilization of the process was considered as the treatment outcome. The AFP level as of March 2023 was 9 IU/mL.

Given the stabilization of the tumor process in the lungs and slow growth in the liver, it became clear that the only method that can give a chance for a meaningful prolongation of life could be the removal of the tumor from the liver transplant.

However, under the existing conditions, extensive resection of the right lobe of the liver was impossible due to insufficient functional reserve of the remaining part of the liver: FLR was 599 cm^3 (32%) (Fig. 1); PDR of indocyanine green (ICG) was 12.3%.

In this situation, theoretically, right portal vein (RPV) embolization could promote vicarious hypertrophy of the remaining part of the liver, but the waiting time usually exceeds three to four weeks. At the same time, there was no understanding of how the graft would behave. Besides, the RPV was already blocked by the tumor at that moment (Fig. 2), i.e. hypertrophy had already taken place, but it was obviously insufficient.

In this situation, the only option for surgical intervention was, in our opinion, two-stage hepatectomy using the ALPPS procedure. It is known that the positive side of this technique is that it achieves vicarious hypertrophy

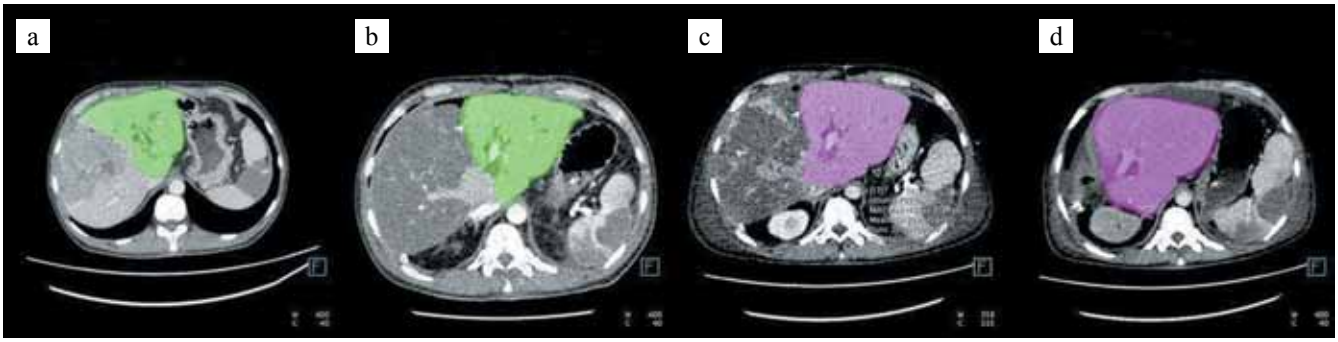

Fig. 1. Perioperative CT liver volumetry with assessment of FLR, highlighted in green/purple: a, preoperative CT volumetry on April 11, 2023; FLR volume is 599 cm^3 (32%), highlighted in green; b, CT liver volumetry on April 19, 2023 (postoperative day 1 from the first stage of two-stage transplant hepatectomy); FLR volume is 649 cm^3 (35%), highlighted in green; c, CT liver volumetry on April 23, 2023 (postoperative day 5 from the first stage of two-stage transplant hepatectomy); FLR volume is 799 cm^3 (43%), highlighted in purple; d, postoperative CT liver volumetry on May 02, 2023 (postoperative day 9 from the second stage of two-stage transplant hepatectomy); FLR volume is 1244 cm^3, highlighted in purple

in the remaining part of the liver in a fairly short period of time – up to two weeks – and allows for optimizing the time of the second stage.

The first stage was performed on April 18, 2023. Considering that such graft resections have not been previously described in the available literature, we consider it necessary to describe in detail the course of the surgical intervention.

Laparotomy was performed with excision of the old postoperative scar using a Rio Branco type approach. No ascites or carcinomatosis were detected in the abdominal cavity. There was a pronounced fibrotic process after the previous LT. With significant technical difficulties, the right and left liver lobes were isolated from the adhesions. The right lobe of the liver was mobilized before the donor conduit of the right inferior vena cava (IVC) and piggy-back caval anastomosis were visualized. The mouth of the right hepatic vein of the liver graft was visualized at its caval hilum. In the right lobe of the liver, occupying practically all its segments, with the largest volume mainly in segment 8 with partial extension to segment 4a, there was a multinodular neoplasm measuring up to 15 cm of dense consistency (Fig. 3). There was also a pronounced fibrous-adhesive process in the hepatic-duodenal ligament. When dissecting its elements, the first step was to isolate the hepatic artery in the zone of division into right and left. The right lateral wall of the portal vein and the bile duct were differentiated with technical difficulties. Between the bile duct and the portal vein on its anterior wall, there was a lymph node measuring up to 3 cm in size, suspicious for tumor. With pronounced technical difficulties, the bile duct was isolated, taken on a "holder", which allowed to perform lymphadenectomy from the anterior wall of the portal vein. The portal vein was isolated up to the fork into the right and left lobar veins. Its right branch (Fig. 4) was ligated. The appearance of demarcation along the Cantlie line was noted. Intraoperative Doppler ultrasound was performed. The study noted that the tumor node spread to the siva and was located in the basins of the right and

Fig. 2. Contrast-enhanced abdominal CT scan on April 11, 2023 (frontal slices). The right branch of the portal vein is blocked by a tumor, indicated by red arrow

Fig. 3. Intraoperative photo (first stage of two-stage transplant hepatectomy). Multinodular neoplasm (hepatocellular carcinoma) of the right lobe of the liver graft

middle hepatic veins, while the mouth of the middle hepatic vein was free of the tumor process. A decision was made to dissect the parenchyma 1 cm to the right of the trunk of the middle hepatic vein, while preserving its orifice. Using monopolar and bipolar coagulators, water jet dissector with alternate ligation and suturing of significant vascular-secretory elements, the liver parenchyma was dissected (Fig. 5) up to the fibrous plate of the portal vein. Hemostasis was performed by argon-plasma and bipolar coagulation, using hemostatic agent Surgicel. The operation was completed by abdominal drainage and layer-by-layer suturing of the postoperative wound. The first stage lasted for 340 minutes, blood loss was 500 mL.

The postoperative period was characterized by extremely pronounced cytolytic syndrome, increasing markers of systemic inflammatory reaction (C-reactive

protein, procalcitonin), as well as significant renal failure (Table).

Fig. 4. Intraoperative photo (first stage of two-stage transplant hepatectomy). The right lobular branch of the portal vein on a black ligature. The right lobular bile duct is on a yellow rubber band

Taking into account the pronounced progression of encephalopathy, respiratory failure, with the need for mechanical ventilation, anuria and the need for renal replacement therapy (RRT), increasing dosages of vasopressor drugs on day 5, indications for the second stage were set. At the same time, based on the results of control CT liver volumetry conducted on April 23, 2023, the volume of the remaining part of the liver increased from 599 ml to 799 ml (Fig. 1).

The second stage was performed on April 23, 2023. Revision of the abdominal cavity revealed up to 500 mL of clear ascitic discharge without signs of infection, and small volume of blood clots (up to 100 ml). Moderate adhesions (Fig. 6). The removed liver parenchyma was bluish in color and had a soft-elastic consistency. The remnant liver parenchyma had visually physiological color and consistency, somewhat edematous, increased in volume (hypertrophy) in comparison with that of April 18, 2023. Adhesiolysis was performed with technical difficulties. The right hepatic artery was crossed between ligatures. The right branch of the portal vein was re-ligated and crossed. The portal fibrous plate was crossed between two clamps and the remaining part was sutured. The right hepatic vein was isolated with application of a vascular clamp on its orifice. The drug was removed.

Fig. 5. Intraoperative photo (first stage of two-stage transplant hepatectomy). Dissection of the liver graft parenchyma with a water-jet dissector along the branch of the middle hepatic vein (indicated by yellow arrow)

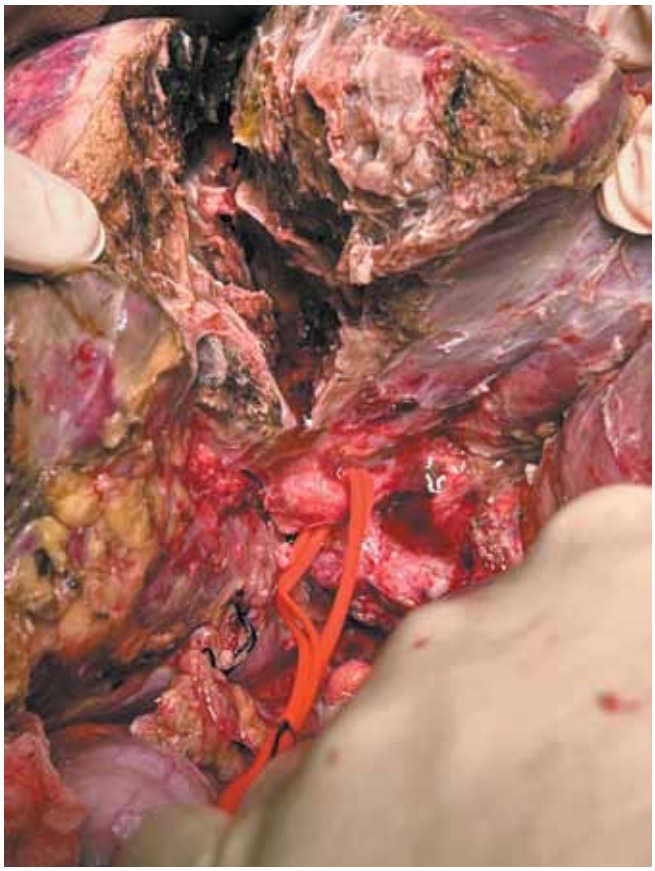

Fig. 6. Intraoperative photo (second stage of two-stage transplant hepatectomy). Moderately pronounced abdominal adhesions. The right hepatic artery is on a red rubber band

The resection plane was treated with argon-plasma and bipolar coagulation (Fig. 7), Surgicel plates were installed. The mouth of the right hepatic vein was sutured. The operation was completed with abdominal drainage and layer-by-layer suturing of the postoperative wound.

The postoperative period at the end of the second stage was complicated by renal failure requiring continuation of RRT (Table), with its subsequent transfer to intermittent mode and periodic episodes of encephalopathy managed conservatively.

The patient was discharged for outpatient treatment 45 days after the first stage of surgical intervention.

The follow-up period so far has reached three months, there is no data on tumor progression.

Fig. 7. Intraoperative photo (second stage of two-stage transplant hepatectomy). The resection plane of the liver graft after tumor removal and completion of hemostasis (argon plasma coagulation, Surgical plate installed)

DISCUSSION

Despite strictly being within the Milan criteria, HCC recurrence rate was 8% to 20% and usually occurs in the

Table

Dynamics of main laboratory parameters, future liver remnant volume, plasma disappearance rate of indocyanine green and invasive and extracorporeal methods of organ systems support in a 45-year-old patient in the perioperative period during a two-stage transplant hepatectomy by ALPPS technique with hepatocellular cancer progression

	ALPPS stage 1				ALPPS stage 2													
Postoperative day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	21	23
ALT (U/L)	**5462**	**4238**	**2387**	1401	822	508	396	272	206	118	103	68	55	50	57	38	39	35
AST (U/L)	**11,175**	**4650**	**1686**	494	223	373	232	117	87	58	65	53	46	55	73	69	56	29
Bilirubin (μmol/l)	20	21	14	24	25	26	18	13	12	12	13	11	12	9	12	9	8	7
Albumin (g/L)	23	21	20	23	26	28	23	22	22	25	24	20	22	20	21	20	19	17
Quick prothrombin (%)	47	45	60	65	69	51	65	79	73	76	81	78	82	79	75	72	70	63
INR	1.7	1.7	1.4	1.3	1.2	1.6	1.3	1.2	1.2	1.2	1.1	1.2	1.1	1.2	1.2	1.2	1.3	1.4
Creatinine (μmol/L)	162	**370**	**497**	**606**	292	232	254	273	267	258	276	285	451	252	179	220	399	401
Urea (mmol/L)	5	13	19	25	14	11	13	15	15	16	15	17	27	17	13	16	33	42
C-reactive protein (mg/L)	77	**211**	**222**	**213**	**210**	112	110	78	65	60	99	92	104	89	97	107	107	104
Procalcitonin (ng/mL)	–	–	–	**67**	**73**	**63**	–	–	–	–	–	10	–	–	–	–	–	–
Spontaneous diuresis	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	+	+	+
Renal replacement therapy	–	–	–	+	+	+	+	+	+	+	+	+	–	+	+	–	–	–
Ventilator	–	–	–	+	+	+	–	–	+	+	+	+	+	+	+	–	–	–
Future liver remnant volume (mL^3)	599				799									1244				
ICG-PDR (%)	12.3				16.4									21.3				

Note. ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalized ratio; ICG-PDR, indocyanine green plasma disappearance rate.

first 12–16 months after LT [7]. In most cases when a recurrence develops, the prognosis is extremely unfavorable and the median survival from the time of recurrence is between 7 and 16 months [8]. Optimal treatment strategies for post-LT recurrent HCC have not been defined and therapeutic options are limited. In most patients, the disease continues to progress despite therapy. There are rather scarce data in literature on the use of regional therapies for recurrence. In 11 patients with tumor recurrence in the graft after microwave ablation performed, the two-year survival rate was 15%, and the average survival was 17 months [9].

The efficacy of conventional transcatheter arterial chemoembolization (TACE) in 28 patients with recurrent HCC after LT from a living donor was evaluated by Ko et al. [10]. After HCC, the targeted tumor reduced in size by ≥25% in 19 of the 28 study patients (67.9%). However, intrahepatic recurrence or extrahepatic metastasis occurred in 92.9% of patients during the 6-month period following TACE. Moreover, long-term prognosis was extremely poor, with 1-, 3-, and 5-year survival rates of 47.9%, 6.0%, and 0%, respectively, and a mean survival of 9 months [10].

The median overall survival for the sorafenib/regorafenib sequence (counting from the start of sorafenib use) was 28.8 months. All patients receiving regorafenib experienced side effects, but adverse events (above grade 3) were severe in 14 patients (38.9%) [11].

Despite the promising results of immunotherapy, the ability to safely utilize checkpoint inhibitors in the post-transplant setting remains a current challenge. In parenchymal organ transplant recipients, the PD-1/PD-L1 pathway is fundamental in the regulation of alloimmunity and graft tolerance [12]. Thus, using these drugs after transplantation may expose these patients to the risk of graft rejection and graft loss, and in more severe cases this may lead to death [13, 14].

At the same time, it is well established that hepatectomy, when potentially feasible, has a much better outcome compared with palliative methods [4–6]. An Italian multicenter study reported a significantly better 4-year survival rate in patients with resectable recurrences compared to patients with unresectable disease: 57% *vs.* 14% [15]. Undoubtedly, such a radical surgical tactic carries objective difficulties and requires a balanced decision based on assessment and acceptance of possible risks and complications, especially in the absence of wide international experience and clear clinical guidelines. Technical nuances include pronounced adhesions after previously performed LT, undesirability of performing the Pringle maneuver due to the high risk of ischemic cholangiopathy, i.e. resection with preserved blood flow, which requires extreme precision and delicacy of the manipulations performed. Foreign colleagues confirm the difficulties of performing such interventions and postoperative management of such patients, and describe an in-hospital mortality rate of 21.4% [16]. In addition to refined surgical skills, post-LT hepatectomy requires highly skilled patient management in the intensive care unit due to compromised immune status and renal function resulting from immunosuppression with the possibility of adequate antimicrobial therapy and RRT. Nevertheless, most authors agree that such operations are feasible at specialized centers, and one of the main criteria for success is an adequate volume of FLR. And if in planning a primary hepatectomy, the necessary safe FLR is widely known: more than 25–30% of parenchyma without cirrhosis and more than 40–45% with cirrhotic transformation [17], then in the case of post-LT hepatectomy, this figure is not strictly regulated due to the lack of understanding of the regenerative capabilities of the graft. In available reports, statistical calculations are not divided into cohorts based on the volume of hepatectomies performed after LT; therefore, it is extremely difficult to predict the risks of post-hepatectomy liver failure in extended liver resection [4, 6]. In our case, FLR was 32%, which, in our opinion, was an extremely borderline value. For additional risk stratification, liver function was assessed by PDR of indocyanine green (ICG). The PDR was 16.7%/min, which also does not reliably guarantee a safe hepatectomy. We excluded the option of embolization of the right branch of the portal vein due to tumor blocking of the vessel and long waiting time for hypertrophy. In this situation, the only possible option, in our opinion, was a two-stage transplant hepatectomy using the ALPPS procedure. It should be emphasized that in the available literature, there are no cases of such operations performed after LT. An additional factor in favor of ALPPS was the close proximity of the tumor to the middle hepatic vein and the likelihood of extending the resection volume to the 4th segment. Based on our experience, we consider it necessary to use a water-jet dissector when dissecting the parenchyma with preserved blood flow, which ensures accurate and precise manipulations.

An important aspect in terms of perioperative management of the patient, in our opinion, was the complete withdrawal of immunosuppression three days before and after the intervention, given the high risks of septic complications and renal failure. Even so, these complications could not be avoided, but regular monitoring of the flora with antibacterial therapy according to the sensitivity spectrum and RRT according to indications, ensured final success.

CONCLUSION

The prognosis for the recipient's life after LT for HCC is determined not only by the known selection criteria and immediate success of the operation, but also by the effective treatment of recurrence. In large, specialized centers with tremendous experience in LT and hepatecto-

my, active surgical tactics should definitely be considered in case of recurrence in the graft.

We are certainly aware of the fact that the chosen tactics is an operation of desperation. However, if the fundamental principles of liver surgery, anesthetic and resuscitation therapy are observed, this tactic can be successful. The authors are far from thinking that the operation will completely save the patient from further progression of the oncologic process. However, they hope that, considering the addition of drug therapy, it can improve the prognosis for the patient's survival.

The authors declare no conflict of interest.

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