

Allograft Inflow - Concern in Liver Transplantation after Intraoperative Radiotherapy for Cholangiocarcinoma

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Rezumat

Restabilirea fluxul arterio-portal al allogrefei - o problemă dificilă a transplantului hepatic după radioterapie intra-operatorie pentru colangiocarcinom

Pacienții la care s-a asociat radioterapia locală în timpul rezecției chirurgicale pentru colangiocarcinom au un risc crescut de a dezvolta tromboză splanhnică extinsă și ciroză biliară, devenind astfel candidați pentru transplant hepatic. La acești recipienți, restabilirea fluxului portal și arterial al grefei hepatice nu se poate realiza prin tehnici chirurgicale convenționale. Hemitranspoziția cavoportală și anastomoza renoportală, alături de reconstrucții arteriale complexe sunt proceduri inovatoare pentru asigurarea fluxului sanguin aferent al grefei hepatice în asemenea cazuri. Analizăm două cazuri de colangiocarcinom hilar tratat inițial prin hepatectomie stângă-doudenopancreatectomie Whipple – în bloc și radioterapie intraoperatorie, care au dezvoltat tardiv ciroză biliară secundară postradică, necesitând ulterior transplant hepatic. În timpul procedurilor au existat dificultăți majore legate de tromboza splanhnică extensivă și leziunile peritoneale post-radice. S-a practicat hemitranspoziție cavoportală, respectiv anastomoza porto-renală stângă, alături de reconstrucții complexe arteriale hepatice. Pacienții au supraviețuit 57, respectiv 18 zile postoperator. Hemitranspoziția cavoportală și

anastomoza portorenală sunt proceduri chirurgicale practicate de necesitate în transplantul hepatic pentru situația trombozei splanhnice difuze arteriale și venoase indusă de radioterapia intraoperatorie anterioară. Această condiție influențează nefavorabil supraviețuirea pacientului și a grefei hepatice datorită ratei crescute a complicațiilor vasculare și biliare, astfel încât acești pacienți nu sunt preferabili pentru transplant hepatic.

Cuvinte cheie: colangiocarcinom, hemitranspoziție cavoportală, anastomoză reno-portală, transplant hepatic, tromboză splanhnică extensivă

Abstract

Patients who underwent local radiotherapy during surgical resection for cholangiocarcinoma are at increased risk of developing extensive thrombosis of splanchnic vessels and secondary biliary cirrhosis on the remnant liver; hence they become liver transplantation candidates. In these recipients, adequate graft inflow cannot be provided by conventional liver transplantation procedures. Cavoportal hemitransposition and renoportal anastomosis alongside complex arterial reconstructions are innovative techniques to restore allograft inflow in such cases. We report two cases of hilar cholangiocarcinoma formerly treated by left hepatectomy-Whipple en Bloc and intraoperative radiotherapy that developed late secondary biliary cirrhosis requiring liver transplantation. During transplant procedure, concern has been raised by the previous radiation-induced peritoneal injury with extended splanchnic thrombosis. Cavoportal hemitransposition and renoportal anastomosis were performed respectively, beside arterial graft reconstructions. Patients survived 57 and 18 days respectively,

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after transplantation. Cavoportal hemitransposition and renoportal anastomosis likewise complex arterial reconstructions are life-saving procedures to secure allograft inflow in the setting of radiation-induced extensive splanchnic thrombosis. However, this condition adversely affects patient and graft survival owing to high rates of early vascular and biliary complications, so these patients are not good liver transplantation candidates.

Abbreviations: CCA - cholangiocarcinoma, CPHT - cavoportal hemitransposition, Ct - celiac trunk, DSVT - diffuse splanchnic vein thrombosis, HA - hepatic artery, IVC - inferior vena cava, LRV - left renal vein, LT - liver transplantation, PV - portal vein, PVT - portal vein thrombosis, RISC - radiation induced sclerosing cholangitis, RISC-BC - radiation induced sclerosing with biliary cirrhosis, RPA - renoportal anastomosis

Key words: cholangiocarcinoma, cavoportal hemitransposition, renoportal anastomosis, liver transplantation, extensive splanchnic thrombosis

Introduction

Surgical resection was widely accepted as conventional treatment for hilar cholangiocarcinoma (CCA) (1) and is frequently associated to Whipple's procedure and intraoperative iridium irradiation. Patients who have ever undergone this treatment carry the risk to develop radiation-induced liver and peritoneal injury leading to clinical events many years after irradiation (2, 3,4). That results in extensive vascular thrombosis both of the venous or arterial splanchnic system and in late radiation-induced sclerosing cholangitis with biliary cirrhosis (RISC-BC) (3,4,5). Therefore these patients frequently come to be liver transplantation (LT) candidates.

Successful LT requires an adequate portal and arterial flow to the graft. However, the incidence of portal vein thrombosis (PVT) at the moment of LT has been reported to vary between 2 and 35 % (6,7,8). In the eighties, even segmental PVT was a contraindication for LT. The progress of adapted surgical techniques such as venous eversion thrombectomy, vascular interposition grafts and the use of portal vein (PV) collaterals, allowed performing successfully LT in such patients (6,7). Diffuse splanchnic venous thrombosis (DSVT) however still remained for a long time a technical contraindication to the transplant procedure, leading finally to the introduction of combined liver-intestinal transplantation as the ultimate solution to overcome this difficult situation (9).

Starzl originally reported in 1973 the use of cavoportal hemitransposition (CPHT) (10,11). His described technique was modified in 1998 by Tzakis implying an end-to-end anastomosis between the native inferior vena cava (IVC) and the graft PV or a side-to-end anastomosis between both vessels followed by a calibration or clipping of the IVC lumen (12). The renoportal anastomosis (RPA), first described by Sheil in 1997 (13), was also modified by Azoulay and Kato using a venous interposition graft

between renal vein and allograft PV (14,15). Both procedures aim to procure a sufficient graft PV inflow.

Arterial splanchnic thrombosis in LT recipients with DSVT renders even more difficult to restore allograft inflow in the setting of a previous radiation-induced peritoneal injury. This point is important because the surgeon who has to operate such patients is faced with major technical difficulties. We report two cases of CCA previously treated by left hepatectomy-Whipple En bloc and intraoperative radiotherapy that developed extensive splanchnic thrombosis and late RISC-BC requiring LT.

Case 1

A 38-year-old Caucasian man with a past history of CCA (with no evidence of primary sclerosing cholangitis) treated by left hepatectomy-Whipple En bloc with hepatic artery (HA) and PV reconstruction, intraoperative loco-regional irradiation and chemotherapy afterwards (8 years before), presented with fatigue, painless jaundice, severe pruritus, dark colored urine, weight loss, ascites. The patient had negative viral or autoimmune serology and metabolic markers. His serum carbohydrate antigen CA 19-9 was normal. Laboratory data showed elevation in serum alkaline phosphatase, gamma glutamyl transferase, five prime nucleotidase and conjugated bilirubin. Serum α -fetoprotein was normal. Doppler ultrasound noticed DSVT and HA thrombosis. MRC showed diffusely dilated intrahepatic ducts with multiple biliary strictures. CT confirmed DSVT and celiac trunk (Ct) thrombosis and the absence of CCA recurrence. Liver biopsy revealed cholestasis, cholangitis and fibrosis, consistent with RISC. Taken together, data concluded the diagnosis of RIBC, DSVT and Ct thrombosis. The patient was listed and transplanted 15 months later (Child A-6 points, UNOS 3, MELD 11). He received a full-sized allograft from a deceased donor. IVC sparing hepatectomy was performed without the use of veno-venous bypass. The graft was implanted by a large latero-lateral cavo-cavostomy (Fig.1). Side-to-end CPHT between the infrahepatic IVC of the recipients and donor PV was performed (Fig. 1). The infra-hepatic caval flow was completely interrupted after liver reperfusion just above the level of the cavo-portal anastomosis, using a double range stapling device (Fig. 1), preventing there by the diversion of blood flow from the liver allograft. As the recipient's Ct was thrombosed, arterialisation of the allograft was done anastomosing the graft's Ct to the recipient's right common iliac artery using an iliac artery graft. End-to-side anastomosis between donor's common bile duct and recipient's already existing Roux-Y jejunal loop was undertaken. The procedure was very bleeding and difficult. Operative time was 20 h and 18 min, cold and warm ischemia time were 19 h 55 min and 23 min, respectively. Auto-transfusion and colloid administration were respectively 3,481 ml and 11,600 ml. Immunosuppression was initiated with tacrolimus and methylprednisolone (4 days) and continued with tacrolimus monotherapy afterwards. The patient required surgical revision the day after LT because of intraperitoneal bleeding. Initial poor function of the graft with major cholestasis has

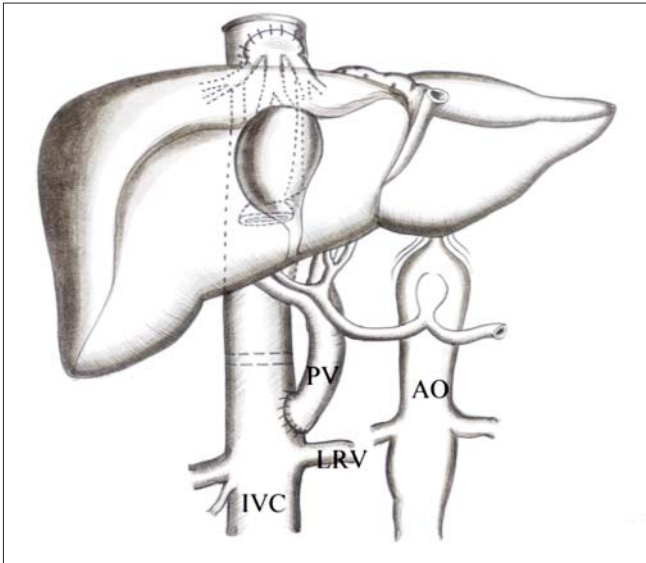


Figure 1. Cavoportal hemitransposition (IVC - inferior vena cava, PV - portal vein, LRV- left renal vein, Ao -aorta)

been observed (since day 2 after LT), with hepatic and renal failure requiring hemodialysis. This surgery was complicated by abdominal wall and ascites infection with streptococcus viridians and enterococcus faecium on day 9 in the post-operative course, resulting in evisceration with multiple surgical revisions and prosthetic repairs. Nineteen days after LT the liver graft biopsy revealed important destruction of hepatocytes and vanishing bile ducts. Seven days later, the graft biopsy showed fibrosis, cholestasis and cholangitis. A CT scan (39 days after LT) disclosed extensive thrombosis of the IVC beneath the renal veins. Finally, the patient developed acute onset of skin rash and severe hemodynamic instability since day 55 and he died of septic shock with systemic fungal infection and multiorgan failure, 57 days after LT.

Case 2

A 69-year-old Caucasian man with a past history of arterial hypertension, hilar CCA treated by left hepatectomy - Whipple en Bloc and intraoperative radiotherapy (5 years before), RISC-BC (4 years before), percutaneous gastrostomy (2 years before), ascites followed by TIPSS (1 year before), acute recurrent cholangitis with septic shock (3 months before), presented with jaundice, pruritus, ascites, encephalopathy, cachexia. Viral or autoimmune serology was negative. No previous evidence of primary PSC or elevated tumoral markers were retained. Laboratory tests showed elevation in serum cholestasis enzymes and conjugated bilirubin. Abdominal ultrasound revealed no dilatation of intrahepatic biliary tree and no evidence of recurrent CCA. Doppler ultrasound disclosed DSVT and Ct thrombosis, alongside a partial thrombosis of the infrahepatic IVC (Fig. 2). MRCP showed diffuse vanishing intrahepatic bile ducts with multiple biliary strictures. Histology subsequently confirmed the RISC-BC and the patient was listed for LT (Child B-9 points, UNOS 3, MELD 15). Ten months after, he underwent LT with a reduced liver (segm I, IV-VIII) from a deceased donor. The hepatectomy was

undertaken with IVC preservation without veno-venous bypass. Large side-to-side cavo-cavostomy was performed. As a result of previous radiation induced damage, the native IVC was covered by a thickened, hemorrhagic peritoneum, rendering its use impossible for CPHT. In the setting of DSVT, the portal graft inflow was secured by an end-to-end anastomosis between the recipient's left renal vein (LRV) and allograft PV (RPA) (Fig. 3), using an iliac vein interposition graft (Fig. 4). Graft portal flow was 200 ml/min. Recipient's HA was thrombosed so the arterialisation of the graft was provided by an interposition conduit fashioned of the superior mesenteric and iliac arteries (from the same donor) between the donor's Ct and the recipient's left common iliac artery (Fig. 4). Complex portal and arterial reconstructions were placed in retrogastric and prepancreatic position (Fig. 3). Temporary external biliary drainage was preferred to a biliary reconstruction in a first step. The difficult and prolonged hemostasis demanded the use of 4 laparotomy towels and temporary abdominal closure. Operative time was 19 h and 17 min. with cold and warm ischemia time of 1,003 and 77 min respectively. Autotransfusion and transfusion were 3,500 and 2,510 ml respectively. Colloid administration was 3,500 ml. Immunosuppression was initiated with tacrolimus and solumedrol. The next day the patient underwent a surgical revision to achieve steady hemostasis and to perform end-to-side choledoco-jejunal anastomosis (on the pre-existing Roux-Y loop). Prosthetic abdominal closure completed the operation. Early non function of the graft was ascertained, with absence of the portal flow on Doppler ultrasound, persistent encephalopathy, INR > 7, V factor ≤ 11 %, elevation of serum bilirubin and renal failure requiring dialysis. The patient was listed on "0 code" and retransplanted 5 days after the former LT using a reduced liver (segments I-IV) from a deceased donor. Total hepatectomy was easily performed after clamping HA and PV beneath the previous anastomosis. The previous cavo-cavostomy was resected after the native IVC was clamped laterally and a new side-to-side cavo-cavoplasty was fashioned. End-to-end anastomosis was performed between the donor's portal vein and the existing iliac vein interposition graft (already anastomosed to the recipient's LRV). Arterialisation of the graft was ensured by end-to-end anastomosis between donor's HA and the pre-existing iliac artery graft (formerly connected to the recipient's left external iliac artery). End-to-side choledoco-jejunal anastomosis was also undertaken and a dual mesh abdominal repair completed the procedure. The arterial and portal flow was of 200 and 230 ml/min, respectively, at the end of operation. It took 4 h and 45 min, with cold and warm ischemia time of 7 h, and 50 min respectively. The patient was found to have evidence of PVT 2 days after re-LT without then running hemodynamic instability. Four days later, acute hepatic failure occurred with major cytolysis, increasing INR (>7), serum bilirubin, ammonia, encephalopathy and Doppler ultrasound showing poor HA flow, consistent with HA thrombosis. Emergent surgical revision was decided, allowing Fogarty HA thrombectomy. Liver biopsy retained extensive centrolobular hepatic necrosis. Despite all endeavors, the patient status worsened rapidly and he died of severe hepatic failure 12 days after his first LT.

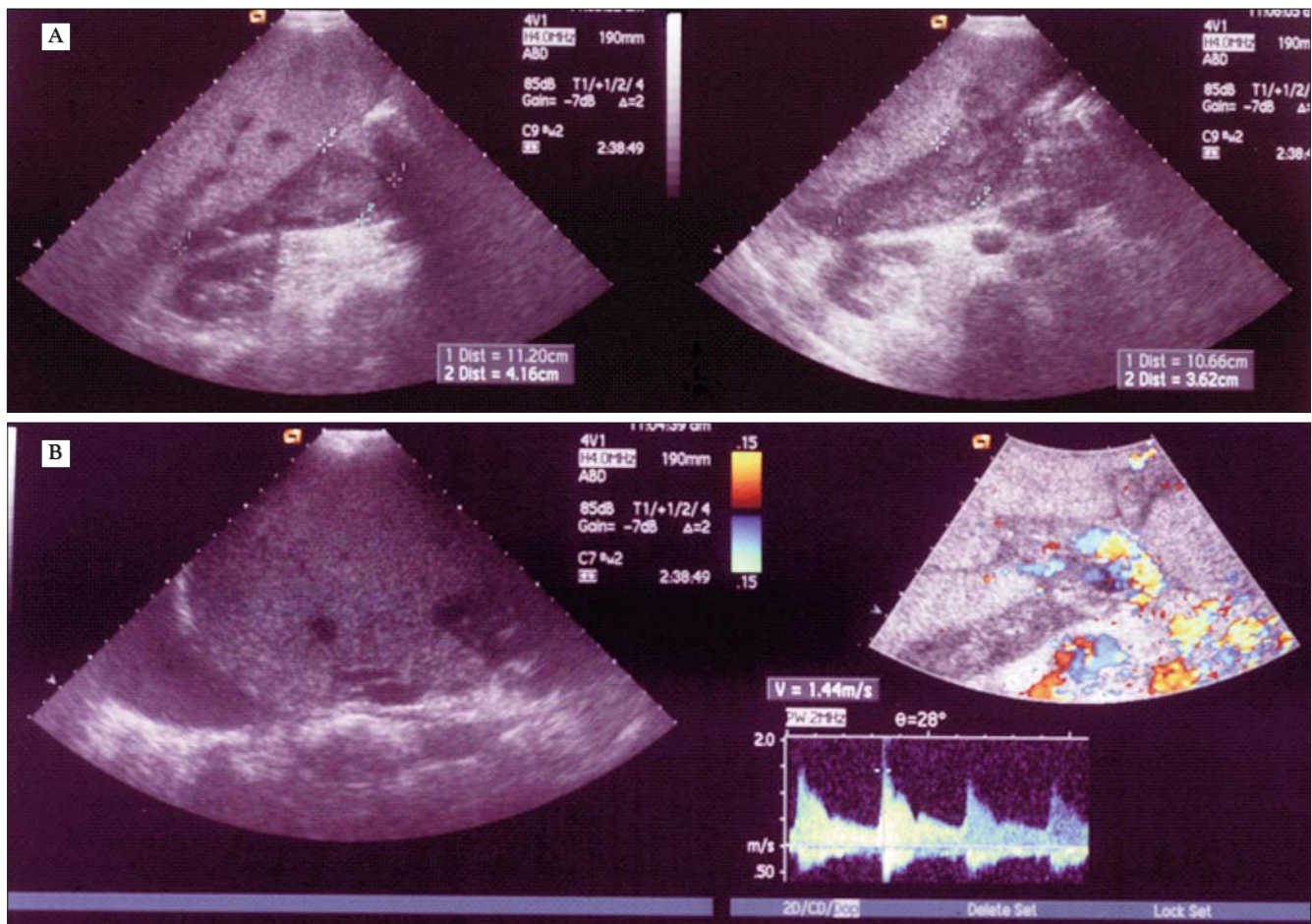


Figure 2. (A, B) Liver ultrasound – extensive portal vein and partial inferior vena cava thrombosis

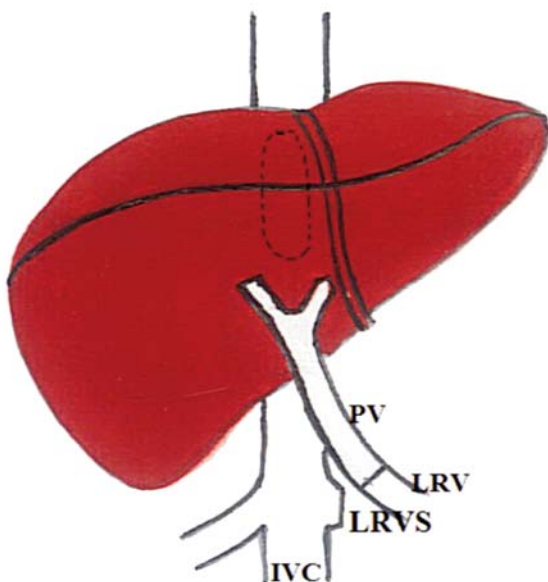


Figure 3. Renoportal anastomosis (IVC - inferior vena cava, LRV - left renal vein, LRVS - left renal vein stump, PV - portal vein)

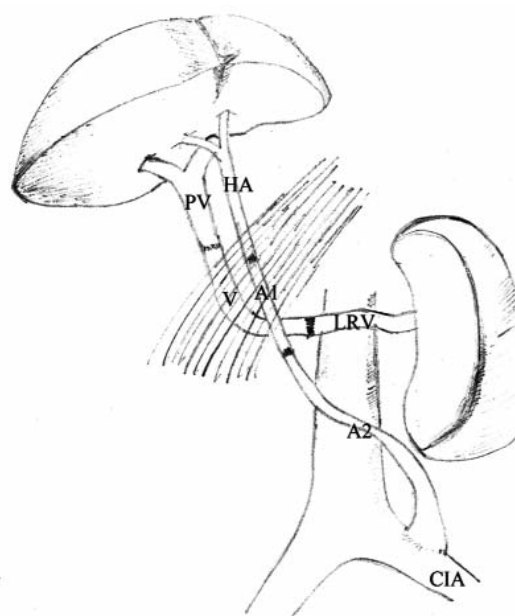


Figure 4. Graft inflow restoring: renoportal anastomosis and complex arterial inflow reconstruction (A1, A2 – arterial graft interposition, CIA – common iliac artery, HA – hepatic artery, LRV – left renal vein, PV- portal vein, V - venous graft interposition)

Discussion

Until recently, surgical resection has been the mainstay of treatment for hilar CCA (1). It affords patients the best chance for short-term survival while the 5-year survival is poor (16,17). Conventional hepatectomy is often associated to Whipple's procedure and intraoperative irradiation (16). Most of so treated patients become LT candidates several years after irradiation because of the well documented (3-5) detrimental effect of radiation therapy on the liver, vessels and peritoneum. The time elapsed between radiation treatment and symptoms ranges from 1 to 10 years (2-5). From a histological perspective, lesions in medium-sized to large vessels ($> 100 \mu\text{m}$ in diameter) express typical features of atherosclerosis, including lipid accumulation, inflammation, thrombosis, increases in intimal thickness and connective tissue content (2,3). Experimental studies have shown that irradiation to bile ducts can lead to progressive obliterative arteritis of small vessels, with subsequent development of ductal fibrosis, biliary strictures and biliary cirrhosis, often requiring LT (2-5). Late effects of radiation also exhibit extensive thrombosis of splanchnic vessels, with DSVT and arterial thrombosis (eg HA and Ct) (2,3).

DSVT represents a great challenge for the transplant surgeon as none of the conventional techniques to overcome PVT is able to solve the problem (18). Different solutions have been proposed in this LT setting. Arterialisation of the PV using an interposition graft between recipient aorta and graft PV is limited in its application as the proper calibration of the arterialisation and the arterial hepatic hyper-perfusion usually seriously compromise the outcome (19-22). The combined liver-intestinal transplantation has been proposed as another treatment modality. The advantage of this type of transplantation, namely to eliminate splanchnic congestion is counteracted by its high morbidity and still poor long-term outcome (3-year survival of only around 50 % in experienced centers)(9). The major short comings of both above mentioned procedures led to the less invasive CPHT. Some 80 cases have been reported so far in the literature (8,12,14,15,18,23). CPHT implies a side-to-end anastomosis, using either a direct approach or an interposition graft, between the recipient's IVC and the donor PV. Azoulay proposed a controlled clipping of the inferior IVC in order to preserve caval as well as hepato-petal flows (14). We further refined the technique in order to avoid well-known thrombotic venous complications. This technique combines IVC sparing hepatectomy and large cavo-caval and cavo-portal anastomosis flush to both sides of the IVC interrupted stapling line. Excellent caval and portal flow can be obtained at both sides of the interrupting IVC, a condition that allows to avoid the formation of (potentially lethal) clots and thrombosis in an otherwise excluded part of the interrupted IVC (11) (Fig. 3). When LTCPHT procedure is impossible, RPA represents an alternative technique to ensure systemic venous allograft inflow (Fig. 4). This technique has the advantage that it doesn't neither interrupt IVC flow nor disconnect existing porto-systemic venous

communications and that it allows retainment of the spleen, an important feature in immunosuppressed patients. Azoulay and Kato advocated RPA as strategy of choice in liver recipients having preexistent spontaneous or surgically constructed splenorenal shunts. RPA has the advantage that left RV and PV are well matched and co-axial venous structures; moreover the physiological retrohepatic IVC flow, which is devoid only of the left RV inflow, remains preserved (14,15). The main drawback of CPHT and RPA lies in their inability to adequately decompress the splanchnic venous system (8,12,14,15,18). Indeed the LTCPHT procedure transforms the condition of DSVT and end-stage liver disease into the condition of DSVT with a healthy liver only.

Our analysis showed the limits of the LT-CPHT/RPA procedures. Both our transplanted patients that have previously underwent left hepatectomy-Whipple en Block and intra-operative radiotherapy, died after LT-CPHT and RPA procedures. They not only presented with DSVT but also with HA thrombosis and pronounced radiation-induced peritoneal injury making the hepatic and abdominal dissection very difficult and even hazardous. We came across a thickened and hemorrhagic peritoneum around the vessels, with a network of dilated collaterals, which entailed major bleeding during the attempted division of adhesions to gain access to the liver, IVC and hepatic pedicle. The impossibility to use the native IVC in case 2 obligated us to perform a RPA to secure portal allograft inflow. Both patients also needed complex arterial graft reconstructions and early surgical revision because of recurrent bleeding and vascular thrombosis. Pre-transplant radiation-induced peritoneal injury represented an additional risk factor for primary non function or initial poor function of the graft due to the prolonged ischemia times resulting from the encountered intra-operative technical concerns. Such technical difficulties were also reported in series of experimental protocols with LT for hilar CCA after neoadjuvant chemo-radiotherapy or after radiotherapy combining LT and total hepatectomy-Whipple En bloc (24-25). LT with neoadjuvant therapy was associated with far higher rates of late arterial and portal complications, but these complications did not adversely affect patient and graft survival (24) unlike our 2 cases which underwent LT several years after irradiation for RISC with hepatic failure.

In conclusion, LT for other wise unresectable CCA should be limited to experimental protocols. Diffuse splanchnic thrombosis is no longer an absolute contraindication for LT. CPHT and RPA likewise complex arterial reconstructions are salvage procedures which may allow adequate graft inflow in these patients. They represent a very valuable alternative to the more aggressive combined liver-intestinal transplantation. In case of RIBC, LT emerged as the only treatment to overcome end-stage liver disease. However, we feel that one should be cautious when considering this treatment modality, because radiation-induced diffuse splanchnic thrombosis impairs patient and graft survival, owing to high rates of vascular and biliary complications.

Conflict of interests

There is no conflict of interests.

Acknowledgment

Illustration 1, 3 and 4 by M. Gheteau.

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