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DISSERTATION

Imaging-based Planning of Portosystemic Shunt Surgery

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II List of abbreviations in alphabetical order

A	- artery
CT	- computer tomography
EGD	- esophagogastroduodenoscopy
EHPO	- extrahepatic portal vein obstruction
ES	- end-to-side
HVPG	- hepatic venous pressure gradient
IVC	- inferior vena cava
MC	- mesocaval
MRI	- magnetic resonance imaging
O1	- most experienced observer
O2	- least experienced observer
PC	- portacaval
PHT	- portal hypertension
PS	- portosystemic
PSSS	- portosystemic shunt surgery
PTFE	- polytetrafluorethylen
PV	- portal vein
ROC	- receiver operating characteristic
RV	- left renal vein
SMV	- superior mesenteric vein
SR	- splenorenal
SS	- side-to-side
SV	- splenic vein
TIPS	- transjugular intrahepatic portosystemic shunt
V	- vein

III . I Abstract

Introduction: Due to the increasing use of minimally invasive radiological approaches to portosystemic shunting as a therapeutical option for portal hypertension (PHT), the once preferred portosystemic shunt surgery (PSSS) seems to be on the decline. However, under certain conditions this surgical approach is still the most appropriate or the only suitable option to create a portosystemic shunt. The surgeon is faced with the challenge of decision-making for a type of surgical shunt which should not only be the best possible procedure but also a surgically possible one for any individual patient.

Preoperative planning based on CT or MR imaging is essential for predicting the most suitable and promising shunting option and hence improving the outcome while reducing the procedure time and invasiveness of the surgical intervention by avoiding intraoperative exploration. However, the reliability of these methods for identification of an appropriate surgical technique has never been proven.

The aim of this retrospective study was therefore to evaluate the accuracy of vascular imaging using CT and MRI as a preoperative planning method for portosystemic shunt surgery in patients unsuitable for transjugular intrahepatic portosystemic shunt (TIPS).

Methods: We retrospectively analyzed the CT and MRI preoperative images of forty-four patients who had had portosystemic shunt surgery at our institution. These images were independently and semi-blindedly analyzed by two observers (O1, O2) with different levels of experience. Each observer recommended two shunting techniques based on clinical and anatomical information. These recommendations were then compared with the shunt performed by the surgical team and its outcome was interpreted.

Results: The two shunts recommended by the two radiologists included the PSSS performed in 88%/100% (CT/MRI, O1) and 76%/73% (O2); if the type of anastomosis was taken into account, these were included in 79%/73% (O1) and 67%/60% (O2). Surgical procedures with added complexity (due to anatomical particularities or vessel distance) were predicted in 87% (sensitivity 80%; specificity 96%). Larger shunt vessel distances were associated with therapy failure ($p = 0.030$) and a vessel distance of ≥ 20 mm was identified as the optimal cut-off in which a graft interposition was used. No statistically significant difference between MRI and CT in predicting the intraoperative decisions ($p = 0.294$ to 1.000) was found.

Conclusion: Preoperative interpretation of CT and MRI imaging through an experienced radiologist can be a helpful guide for surgeons in preoperative planning of PSSS. Information necessary to identify technically feasible variants and complicating factors can be obtained from this analysis, hence contributing to a better surgical outcome.

III . II Zusammenfassung

Einleitung: Neue minimalinvasive radiologische Ansätze für portosystemische Shuntverfahren zur Therapie der portalen Hypertonie (PHT), konkurrieren mit der portosystemischen Shunt-Chirurgie (PSSS). Unter bestimmten Bedingungen ist die Chirurgie jedoch weiterhin die geeignetere oder einzige Möglichkeit.

Der Chirurg stellt sich bei der Indikation der Herausforderung, welches portosystemische Shunt-Verfahren für den einzelnen Patienten technisch möglich und angemessen ist. Die präoperative Planung mit erweiterter Bildgebung in Form von Computertomographie (CT) oder Magnetresonanztomographie (MRT) ist essentiell bei der Entscheidung für ein bestimmtes Shunt-Typen. Bessere Ergebnisse sowie kürzere Operationszeiten und Invasivität des chirurgischen Eingriffs können erzielt werden bzw. eine unnötige intraoperative Exploration kann vermieden werden. Bisher wurde die Zuverlässigkeit dieser Methoden bei der Identifizierung einer geeigneten Operationstechnik jedoch nicht geprüft.

Ziel dieser Studie war es den Stellenwert von CT und MRT zur präoperativen Planung für die Genauigkeit der Gefäßdarstellung vor portosystemischer Shunt-Chirurgie bei Patienten zu bewerten, die für eine TIPS ungeeignet waren.

Methoden: Wir analysierten retrospektiv präoperative CT- und MRT-Bilder von vierundvierzig Patienten, die in an der Chirurgischen Klinik der Charité–Universitätsmedizin Berlin am Campus Virchow Klinikum eine portosystemische Shunt-Operation erhielten. Deren Bildgebung wurden unabhängig und halb verblindet von zwei Radiologen (Beobachter bzw. Oberserver 1 und 2 (O1, O2)) analysiert, die unterschiedlich im beruflichen Ausbildungsstand waren (O1 als Leitender Oberarzt im 2. Berufsjahr, O2 im 3. Weiterbildungsjahrs als Assistenzärztin) Erfahrungsniveaus analysiert. Jeder der beobachtenden Radiologen empfahl zwei Shunt-Techniken basierend auf klinischen und anatomischen Informationen, die anhand der Bildgebung geschlussfolgert werden konnten. Diese Empfehlungen wurden retrospektiv mit dem durchgeführten Shunt verglichen und das Ergebnis interpretiert.

Ergebnisse: Die beiden von den Radiologen empfohlenen Shunts umfassten die durchgeführten PSSS in 88%/100% (CT/MRT, O1) und 76%/73% (O2) der Fälle; wenn die Art der Anastomose berücksichtigt wurde, waren diese in 79%/73% (O1) und 67%/60% (O2) enthalten. Chirurgische Eingriffe mit zusätzlicher Komplexität (aufgrund anatomischer Besonderheiten oder Gefäßentfernung) wurden in 87% vorhergesagt (Sensitivität 80%; Spezifität 96%). Größere Distanzen zwischen den Shunt-Gefäßen waren signifikant häufiger mit Therapieversagen assoziiert ($p = 0{,}030$). Ein Gefäßabstand von ≥ 20 mm wurde als optimaler cut-off identifiziert, bei dem eine Transplantatinterposition verwendet wurde. Es zeigten sich keine

statistisch signifikanten Unterschiede zwischen MR und CT die Prädiktion der intraoperativen Entscheidungen (p = 0,294 bis 1.000) betreffend.

Schlussfolgerung: Die präoperative Interpretation der CT- und MR-Bildgebung für die Indikationsstellung bei der Auswahl der Shunt-Art durch einen erfahrenen Radiologen, kann die Erfolgsquote PSSS unterstützen. Diese retrospektive Analyse könnte zur Identifizierung technisch realisierbarer Varianten und komplizierender Faktoren hilfreich sein und zu einem besseren chirurgischen Ergebnis beitragen.

IV Introduction

IV . I Cross-sectional imaging

Diagnostics and therapy in general have been revolutionized in the last 40 years through the introduction of cross-sectional imaging, with which the ability to image the body in two-dimensional, axial views of gross anatomical structures seen in transverse planes is achieved. In this work computer tomography (CT) and magnetic resonance imaging (MRI) play a pivotal role. Both allow the acquisition of cross sections and hence the visualization of tissues and organs in two dimensions.[1]

In the context of PHT, if used properly, both CT and MRI can have a crucial role, e.g. in detection of portal vein or inferior vena cava thrombosis and resultant changes in liver morphology and enhancement patterns, venous collaterals, varices, and ascites, as well as postoperatively in evaluating patency of surgical portosystemic shunts.[1]

IV . I . I Computer tomography

CT is acknowledged as the biggest step forward in radiology ever since the discovery of x-radiation. It is a computer-assisted radiographic method that allows the imaging of the human body in cross sections. Modern computer tomographs use a rotational system, with an x-ray beam emitter and a receiver placed facing each other. Radiation is sent in a circular perpendicular direction to the body axis and is registered through the detection system on the other side. The different absorption profiles are presented through a tissue specific attenuation coefficient in different shades of grey and are therefore possible to interpret.[2]

With the evolution of CT technology, spiral CT and multislice spiral CT followed the first versions and allowed a quicker and continuous image acquisition, reducing motion artefacts, as well as allowing a better presentation of the visceral blood vessels.[3,4] Further advantages include a fast accurate acquisition of spatial information. As disadvantages one can list the radiation imposed on the patient and are sub-optimal soft tissue imaging.

Through contrast-enhanced multiphasic CT, an exact distinction of the vessels of the liver and portal system is made possible. With the different absorptions of radiocontrast agents in the arterial, portal venous and venous phases, a further differentiation of the types of tissue also becomes possible.

Another example of the capabilities of contrast-enhanced CT is the fact that it allows the visualization of the extent of thrombosis (with increased attenuation in the portal vein on unenhanced scans and a lack of enhancement after administration of IV contrast medium) and mapping of the portosystemic collaterals for possible interventions in patients with portal vein thrombosis or cirrhosis.[5]

IV . I . II Magnetic resonance imaging

MRI technology has allowed an immense advance in the presentation of soft tissues of the human body in radiological diagnostics. It is, in comparison to CT, an X-ray-free imaging technology and based instead on the principle of nuclear magnetic resonance. The resonant excitation of protons in the body is achieved by a magnetic field as well as by magnetic alternating fields with high-frequency impulses. After that, electrical signals are induced and ultimately received and localized by means of magnetic gradient fields for further processing and image presentation.

The high contrast of soft tissue, which is the basis for different relaxation times of different tissue types, is very advantageous in radiological diagnostics, when compared to CT technology. The imaging done to date, however, is slower than that of CT, which brings with it image distortion and imaging artefacts.

Referring back to the example of acute thrombosis, it manifests on MRI as an area of abnormal signal within the vessel lumen. On T1-weighted images, a thrombus may be detected as isointense or hyperintense to muscle.

In both CT and MRI, a thrombosed portal vein may be dilated with acute nonenhancing thrombus and may be associated with edge enhancement of the vein because of blood flowing around the thrombus. These two imaging resources can also be used to confirm the presence of chronic portal vein thrombosis, showing an obliterated or attenuated vessel with incorporation of clot into the wall, possibly with linear areas of calcification within the thrombus.

This serves as a mere example of the various features of portal hypertension that CT and MRI are able to depict, including ascites, splenomegaly, and spontaneous portosystemic shunts, such as in patients with of liver cirrhosis.[5-7] As portal vein thrombosis is no longer seen as an absolute contraindication to liver transplant, CT and MRI are also of utmost importance in surgical planning with particular attention to the patency of the portal venous system, including the superior mesenteric and splenic veins.[5]

IV . II Portal hypertension

IV . II . I Definition

The portal vein (vena portae) carries around 1.5 L / min of blood from the small and large intestine, spleen, pancreas, gallbladder and stomach to the liver.[8] PHT is a clinical syndrome hemodynamically defined by an increased portal vascular resistance and/or an increased splanchnic and portal blood flow. In addition, there is a permanent increase of the portal vein pressure (to values >7 mmHg)[9] and/or the portosystemic pressure gradient at any point of the portal venous system (i.e. between the PV and the IVC). In practice, this hepatic venous pressure gradient (HVPG) is calculated by measuring the free pressure and wedge pressure, the upper limit of which is 5 mmHg.[10] A normal HVPG is 3-5 mmHg and clinical relevance starts at 10 mmHg. This gradient predicts a clinical course and development of the following symptoms: esophageal varices, ascites and hepatic encephalopathy.[11,12] In the end stages of PHT, a hepatorenal syndrome may occur, which can culminate in kidney and liver failure, with corresponding high mortality rates.[13]

IV . II . II Epidemiology

In Western Europe and North America 90% of PHT is caused by liver cirrhosis; 60% to 70% is mostly due to alcohol abuse. The main cause in Asia is chronic viral hepatitis infections (being the second in Germany) and in Africa and South America it is schistosomiasis infections.[9,14] The incidence of PHT is much higher in developing countries than in developed countries.[15]

IV . II . III Etiology and physiopathology

According to Ohm's law, the portal vein pressure (P) is dependent on blood flow (F) and vessel resistance (R) [P = F x R]. In contrast to physiological conditions, e.g. postprandial, where there is a slight and time-limited pressure increase in the portal vein, the permanent change of one of these two components becomes pathophysiologically relevant. Therefore, the two main factors causing PHT are the long-term elevated portal vascular resistance and increased splanchnic and portal blood flow.[9]

Increased portal venous resistance and its classification, in the case of structural changes, is often oriented towards the localization of the cause of resistance. Accordingly, one considers different causes to be prehepatic, intrahepatic or posthepatic, depending on whether the changes are located upstream of the hepatic vessels, in the liver or downstream from these vessels.[9,13]

The most common cause of a prehepatic PHT is extrahepatic portal vein obstruction (EHPO) due to thrombosis, also one main etiology in children.[9] Congenital stenosis or atresia of the PV and compressive tumors are also considered to be causes of prehepatic PHT.

With regard to intrahepatic PHT, the most common examples include alcoholic cirrhosis, schistosomiasis, primary biliary cirrhosis, hemochromatosis, Wilson's disease, and veno-occlusive diseases (e.g. Budd-Chiari syndrome). The causes of intrahepatic PHT can be considered separately, depending on where the changes are located, as presinusoidal (in the region of the portal veins), sinusoidal (in the sinusoids), or postsinusoidal (in the terminal hepatic veins). The difference between these localizations is difficult to determine, since in most cases the increase in resistance can be caused by changes on several tissue levels.

Posthepatic causes include cardiac disorders, e.g. constrictive pericarditis and right heart failure, as well as obstruction of the inferior vena cava and the hepatic vein.[9]

PHT may also be associated with increased splanchnic and portal blood flow. It originates from an imbalance between endothelial and neurohormonal vasodilators and vasoconstrictors. This state, also referred to as splanchnic hyperemia, explains why PHT persists despite the establishment of an extensive network of portosystemic collaterals, which can divert 80% of the portal blood flow. Because of this increased blood flow and vasodilatation, an increased cardiac index and hypervolemia occur, in the sense of a hyperkinetic circulatory syndrome, which is closely related to PHT.[14]

PHT is characterized by an HVPG > 5 mm Hg.[12,13] The response to increased venous pressure is the development of collateral circulations that divert blood flow to systemic veins. These portosystemic collaterals are formed through the opening and expanding of vessels already existing between the portal venous circulation and the inferior and superior vena cava[16] and presumably mediated by VEGF- / PEGF-based angiogenesis.[14] HVPG > 8-10 mmHg leads to esophageal and gastric varices arising from collateral circulation through the gastricae breves and coronariae veins to the azygos vein, and through periumbilical, retroperitoneal, vaginal and hemorrhoidal veins, as well as by intrahepatic shunts and recanalization of the vena umbilicalis.[13,16,17]

As a result of these collateral circuits, PHT is initially alleviated through blood diversion, but as the HVPG continues to increase, it acquires clinical relevance and presents with its known symptoms and complications.

IV . II . IV Clinical presentation

PHT can become life-threatening due to its complications. PHT becomes clinically relevant when HVPG > 10 mmHg is reached. HVPG values between 5 and 9 mmHg can be considered as preclinical PHT.[14]

The main complications of PHT include variceal bleeding, ascites, splenomegaly, hypersplenism, hepatic encephalopathy and spontaneous bacterial peritonitis.

Many collateral venous drainage areas are created as portosystemic shunts to bypass the hepatic circulation, namely the esophagogastric, hemorrhoidal, paraumbilical (e.g. caput medusae) and azygos. These shunts are probably further developed by the opening of collapsed vessels, as well as by angiogenesis. After a first phase in which the pressure is able to be decompressed, the bypass circuits are then no longer able to normalize the PHT, if there is continuous pressure increase.

PHT is per se a multisystemic vascular disease affecting multiple organs. Accordingly, the symptoms are also classified into several levels/systems:

- Splanchnic vascular bed - liver cirrhosis is particularly important in this territory because it causes vasodilatation and decreased responsiveness to vasoconstrictors. Increased splanchnic blood flow, in addition to neoangiogenesis, is followed by the development of esophagogastric varices, hypertensive gastro- and colopathy and bleeding. Consequently, two of the most dangerous complications of PHT follow: esophageal varices rupture with bleeding as well as hepatic encephalopathy, both with very high mortality rates.[14]
- Systemic circulation - PHT is often associated with a hyperdynamic syndrome, resulting in hypotonia, increased cardiac index and decreased vascular resistance. This functional hypovolemia seems to be associated with the still unclear pathophysiology of ascites. Spontaneous bacterial peritonitis may occur because of bacterial translocation to the fluid of preexisting ascites.
- Kidney - due to liver cirrhosis, renal vasoconstriction develops as a result of functional hypovolemia, which leads to hepatorenal syndrome.
- Blood - thrombocytopenia, leukopenia and anemia due to hypersplenism, splenomegaly and increased corpuscular sequestration.

- Mental status - change in blood flow to the brain, as well as vascular reactivity are probably a poor starting point for hepatic encephalopathy,[14] which can present as lethargy, irritability, altered sleep patterns or vigil conditions.

Esophagogastric varices are central in the care and treatment of PHT. They develop as a collateral circulation through the coronaria ventriculi veins over the azygos vein in the lower esophagus and gastric fundus. Rupture of one of these varices (variceal bleeding) is associated with a mortality rate of 10-20 % within six weeks after the first bleeding and risk of recurrence of 60 % within the first two years.[9,14,18,19]

As already shown, it is known that varices develop above an HVPG of 10-12 mmHg and that hemorrhage (as well as ascites) occur only with an HVPG >12 mmHg.[12,19] Rupture of these thin-walled submucosal varices occurs in 30-50% of all patients and is responsible for 70% of gastrointestinal bleeding in patients with PHT. It is the most life-threatening complication of PHT.[12,14,20]

IV . II . V Diagnostics and imaging

IV . II . V . I Clinical signs and laboratory analytical parameters

There are not many early clinical signs of PHT. Ascites, increased abdominal circumference, splenomegaly and caput medusae indicate a late pronounced stage of PHT. Typical laboratory changes, such as leukopenia, anemia, and thrombocytopenia in the sense of ongoing hypersplenism, are also of low specificity. In practice, patients with cirrhosis are examined with additional diagnostic methods, and are frequently evaluated, even if there are no signs of PHT.[9,14]

IV . II . V . II Imaging

Although there are many possible complementary procedures for the diagnosis of PHT, imaging and esophagogastroduodenoscopy (EGD) are amongst the most valuable. With abdominal sonography or color Doppler sonography, one can find the following signs of PHT: parenchymosis and vascular architecture change of the liver in the sense of cirrhosis, ascites, splenomegaly, portosystemic venous collaterals, altered or thrombosed portal, splenic, mesenteric superior and gastric veins, as well as a disturbance in flow direction and velocity (such as a hepatofugal rather than hepatopetal flow) and patency in these vessels.[9]

However, ultrasound imaging is operator-dependent and sometimes challenging, because it depends on the location of the shunt and the presence of an acoustic window for good visualization of the shunt. It may also be difficult to elicit color signal from within a synthetic graft or detect flow within a shunt located deep in the abdomen (e.g. mesoatrial or splenorenal).[1]

CT and MRI angiography allow a clear anatomical spatial representation (as detailed in chapter II.I) and allow, for example, the visualization of portal vein obstruction, presence of solid intraluminal material or portal vein cavernoma as in the case of EHPO.

IV . II . V . III Esophagogastroduodenoscopy

For visualization and evaluation of esophageal and gastric varices, as well as prognosis of possible hemorrhage, the EGD is an essential procedure and the method of choice. In addition, it is also one of the best local therapy methods (through sclerosis or ligature of varices) in PHT. The presence of signs of erosion of the epithelium, e.g. "cherry spots" or large-scale varices is predictive of the risk of variceal hemorrhage.

An EGD should be conducted if PHT is suspected and as well as routine procedure when doing periodic check-ups on a confirmed PHT case.[21]

IV . II . VI Therapy

The therapy of PHT has changed since the 1970s, when surgery was the only option, as now there is a wide array of options. Because of the difficulties of reaching consensus on clinically relevant definitions and on the directions of future research and guidelines, several meetings have taken place since the 1980s with the aim of reaching a common working algorithm.[19] Baveno, a small town in the north of Italy by Lake Maggiore, has been one center for consensus meetings since 1990. The purpose of these meetings is to discuss definitions of key events in PHT and esophageal variceal bleeding, the most recent knowledge of PHT physiopathology, diagnostics and therapy, and to issue evidence-based recommendations for the conduct of clinical trials and therapeutic guidelines.[11,19] The last meeting, Baveno VI in 2015, summarized the therapy of PHT as follows:

Several studies have shown that an HVPG < 12 mmHg is protective for esophageal varices, as they become smaller, thus preventing esophageal bleeding.[21,22] A reduction of $> 20\%$ from its basal level was also shown to have a protective effect against variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome and death.[21,23] The reduction of the

HVPG is the rationale behind PHT therapy, acting as prophylaxis for esophageal variceal bleeding. It can be divided into local or physiopathological targeted therapy (i.e. reducing portal pressure).[14]

The therapy of PHT and respective gastric and variceal bleeding is used in different clinical scenarios: in the case of lack of symptoms, in prevention of variceal development, in prevention of a first hemorrhage, as treatment of acute bleeding and in prevention of recurrent bleeding.[24]

The various therapeutic approaches, of which only the surgical will be explained in detail in this work, are listed in Table 1.

Conservative therapy	- Pharmacotherapy[14,19,25] · splanchnic vasoconstrictors (terlipressin and vasopressin); · inhibitory hormones (somatostatin, octreotide and vapreotide) for acute bleeding; · unselective β-blockers (propranolol and nadolol); · unselective β-blockers with α-activity (carvedilol) also as first line treatment; · intrahepatic vasodilators (isosorbide mononitrate, together with β-blockers[26]); · possible future options: estrogen derivatives,[27] serotonin receptor agonists,[28] statins,[29,30] renin-angiotensin-aldosterone system effective drugs[31]
Interventional therapy	- Endoscopy[14,19,25] · endoscopic sclerotherapy and band ligation, to local (i.e., non-pathophysiological-targeted) therapy; · self-expanding metal stent for variceal bleeding tamponade - Balloon tamponade (maximum 24 hours, in refractory esophageal bleeding) · Sengstaken-Blakemore tube (for esophageal varices); · Linton-Nachlas tube (for fundal varices) for use as a bridging measure - Interventional radiology: · transjugular intrahepatic portosystemic stent shunt (TIPS) with polytetrafluoroethylene (PTFE)-covered stents; · balloon occluded retrograde transvenous obliteration (BRTO), for control of gastric variceal bleeding[32,33]; · transhepatic portal vein and direct variceal embolization[34,35]
Surgical therapy	- Esophagogastric varices devascularization surgery[15,36-38] - Portosystemic shunt surgery · nonselective shunts[39] • portacaval end-to-side[40] • mesocaval end-to-side • coronary caval (Inokuchi shunt) · partially selective shunts[39] • portacaval side-to-side (possibly with interponate: Sarfeh shunt[41])

	• mesocaval side-to-side (possibly with interponate: Drapanas shunt[42]) • splenorenal side-to-side (Cooley shunt) • proximal splenorenal (Linton shunt) · selective shunts[39] • distal splenorenal (Warren shunt[43]) • mesoportal (Meso-Rex) - Liver transplantation (as a curative measure, in the case of liver damage)

Table 1. Therapeutic approaches to portal hypertension

IV . III Portosystemic shunt surgery

IV . III . I Development

The therapeutic possibilities for PHT have greatly increased over the past thirty years. Improvement in drug therapy, development of endoscopic sclerotherapy and ligature, the revolutionizing entry of TIPS in interventional radiology as well as the maturing of liver transplantation have pushed PSSS, once the only possibility in the 1970s, to the background. However, in special patients PSSS is still an option.[44]

One of the first portocaval shunts performed in dogs was published by Eck in 1877.[44] Nobel laureates Pavlov (1894) and Carrel (1912) as well as Starzl were pioneers and accomplished tremendous development in the surgical treatment of PHT.[44] PSSS is used as an option when medication and endoscopic procedures are not sufficient to control acute variceal bleeding, as well as a prophylaxis against recurrent bleeding, when the establishment of a TIPS is contraindicated or impossible. TIPS is usually not used in the treatment of pre- and posthepatic PHT and has its contraindications as well, such as severe cardiac disease, rapidly progressive liver failure, severe hepatic encephalopathy, polycystic liver disease, systemic infection/sepsis or unrelieved biliary obstruction and hepatic malignancy.[20,45-48,49] Specifically, TIPS is not suitable for patients with extrahepatic veno-occlusive disease as well as those with advanced hepatic cirrhosis, due to a high risk of hepatic encephalopathy.

PSSS is also cost-effective and prevents regular hospital admissions, providing a more durable long-term solution when compared to TIPS.[24,50]

Indications for operative procedures are strict, since they require a well-preserved hepatic function and for patients for whom a regular TIPS revision, due to lack of immediate access to medical facilities, could be problematic.[39,44] Liver transplantation is the only definitive and causal therapeutical option for patients with poor hepatic status and here TIPS can be a bridging method.[51]

Colapinto published the first study on TIPS in humans (1982),[52] as a minimally invasive and technically simpler decompression method for patients with advanced liver disease and PHT. Despite the previously documented drawbacks (high rate of in-stent stenosis, stent occlusion and hepatic encephalopathy), the TIPS system has experienced a widening usage, becoming the treatment of choice when it comes to decompression of PHT, while surgical options have been pushed to the background. One of the most important limitations of shunt surgery is therefore the declining know-how and scientific interest.[24,39]

Portosystemic shunts aim to lower the HVPG to minimize variceal bleeding. They are hemodynamically classified as unselective, partially selective or selective, according to the selectivity of hepatopetal flow maintenance. Finally, the choice of which variant to perform depends on different factors, such as liver function and the anatomical situation of vessels with regard to the preoperative imaging patency of the vessels, and the possibility of a future liver transplantation must also be considered when choosing a shunt.[24,39] A portosystemic shunt should only be applied when the liver function is compensated.

IV . III . II Technique

Nonselective portosystemic shunts are anastomoses which promote a complete drainage of the portal as well as mesenteric blood flow into the inferior vena cava. A classic example would be the end-to-side portacaval shunt (Figure 1 B), with which Whipple inaugurated the era of PSSS in 1945.[40] This variant includes a transection of the portal vein below the bifurcation in the porta hepatis and an end anastomosis to the lateral aspect of the infrahepatic inferior vena cava. This shunt form is technically easier to standardize and has a shorter operating time. Due to these factors, as well as to the total decompression of the splanchnic system and esophageal varices, it is a preferred shunt variant in emergencies, when endoscopic management is not successful. In the case of stable liver function, such as Child A and B cirrhosis, this shunt can be well tolerated. On the other hand, the risk of postoperative hepatic encephalopathy and further progression of hepatic failure, with reduced liver perfusion, is significantly higher in Child C. If liver transplantation is under consideration, this variant is not used,[39,48,55] a problem that does not arise in the case of an end-to-side mesocaval shunt.

Partially selective shunts promote the maintenance of a portosystemic pressure gradient and thus a residual blood flow of the portal vein. Examples are the portacaval or mesocaval side-to-side anastomosis (Figure 1 C), optionally with a PTFE interponate (6-10 mm diameter)[42,54], which reduces the portal pressure without loss of liver perfusion. Despite guaranteed portohepatic flow, the side-to-side portacaval shunt comes in conjunction with a hepatofugal flow and danger of hepatic encephalopathy. As a variant to this shunt, an interponate-based portacaval shunt (after Sarfeh) guarantees the reflux of the liver sinusoids as well as the control of ascites. The interponate-based mesocaval shunt (after Drapanas; Figure 1 D) is more frequently preferred when a liver transplantation is foreseen, since it does not require any hilary dissection, as well as in the case of prehepatic thrombosis (of the portal or splenic veins). The disadvantage of these interponates is the risk of kinking and thrombosis of the relatively long interponate. Lastly, the central or proximal splenorenal shunt (after Linton; Figure 1 E), with end-to-side anastomosis between the proximal splenic vein with the left renal vein combined with a splenectomy is no longer recommended mainly due to high thrombosis rates (approximately 50%) and spleen loss.[39,48,53,55]

Selective shunts segregate the down-gradient via the esophageal collaterals from the portal hypertensive system and therefore affect portal perfusion the least, as the flow and pressure in the portal vein are not disturbed, and hence they have been developed as an alternative to avoid encephalopathy. This milestone arose when Warren published the distal splenorenal shunt technique (Figure 1 F) in 1967.[43] This shunt diverts the flow of the esophagogastric collaterals, which are decompressed through the gastric fundus and spleen, through an anastomosis between the terminal splenic and the left renal vein. In addition, both coronary and gastroepiploic veins are ligated. The flow of the portal vein changes, however so that the selectivity of this shunt is gradually lost, especially in cirrhotic patients.[39,48,53] This shunt is particularly useful for patients with esophagogastric varices and for patients with extrahepatic thrombosis (80% of whom have a patent splenic vein).[55]

Interestingly, there are no long-term differences in recurrent bleeding, hepatic encephalopathy or overall survival between the different shunt techniques. This can be partially explained by the loss of selectivity over the years.[44,51]

A special form of PSSS is the mesoportal (Meso-rex) shunt, in which a bypass between the superior mesenteric vein and the left intrahepatic branch of the portal vein (in the Rex recessus) is created. In this sense, this anastomosis is formally not a shunt, but a bypass deriving from the main stem of the portal vein, maintaining the physiological liver function. The anastomosis is preferred with an interponate of the great saphenous vein or typically of the internal jugular vein. Lately, this variant has been seen as the gold standard for children with EHPO.[24,39] The greatest benefit is in that it rescues the physiological liver function through a normal hepatopetal flow, consequently reaching better results with lower rates of hypersplenism, coagulopathies or hyperammonemia and overall positive physical and neurological development when compared to classical portosystemic surgical variants.[56-60]

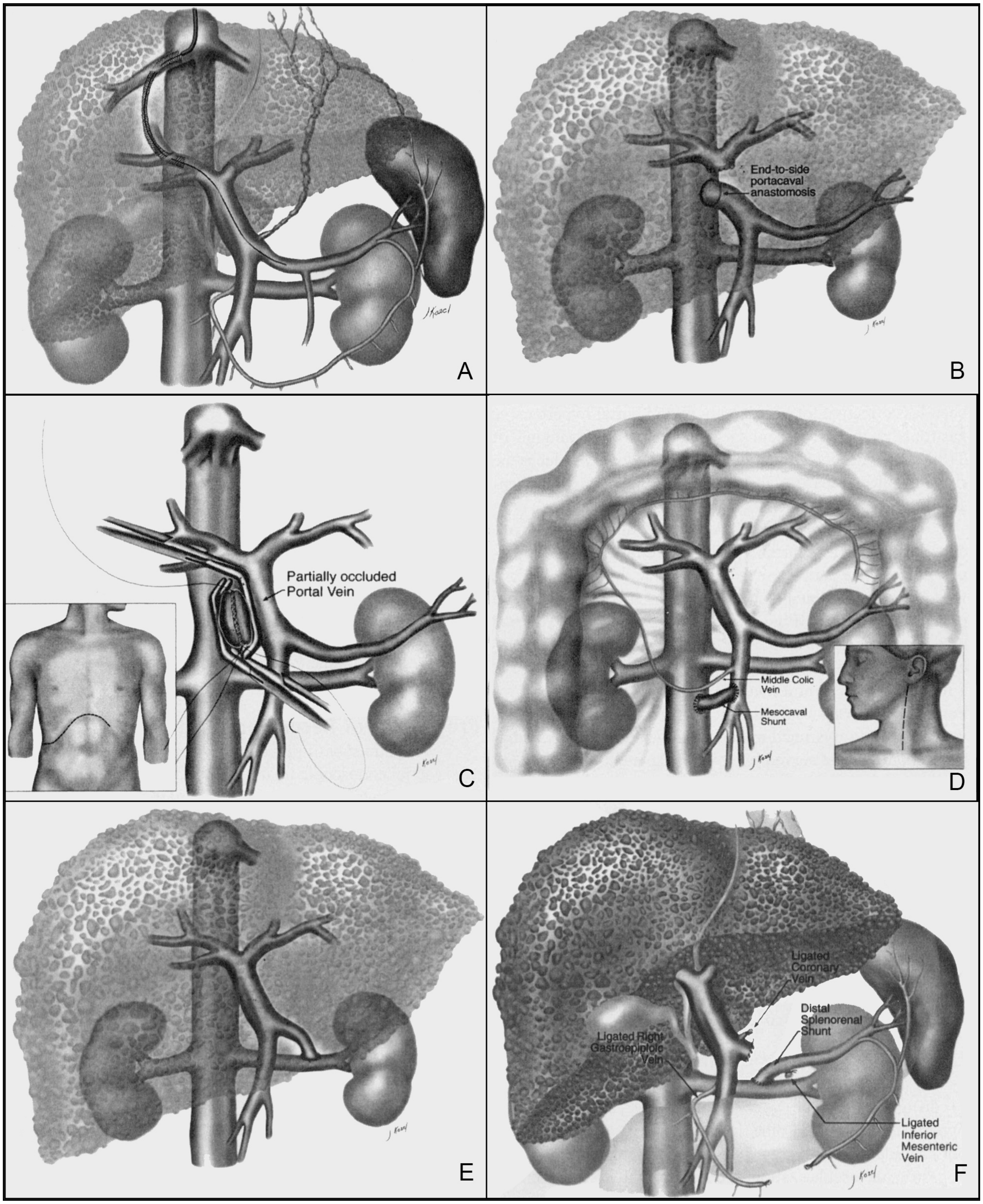

Figure 1. Examples of portosystemic shunts; **A**: TIPS between the right hepatic vein and right branch of the portal vein; **B**: end-to-end portacaval shunt; **C**: side-to-side portacaval shunt; **D**: mesocaval shunt with an interponate; **E**: proximal splenorenal shunt including splenectomy; **F**: distal splenorenal shunt (Reprinted with permission from Knechtle SJ, Portal Hypertension: From Eck's Fistula to TIPS. *Annals of Surgery*. (2003))

V Aim

Therapy of PHT has changed from pure surgical portosystemic shunting as its only possibility in the 1970s to today's wide spectrum of options.

Since the successful introduction of the minimally invasive TIPS procedure, PSSS is seldom chosen. It is, however, an effective therapy variant for specific presentations of PHT. Being highly specialized and surgically challenging, this kind of surgery puts the radiologist in a crucial position in the preoperative planning phase and in choosing the type of PSSS. The aim of this study was to evaluate whether CT and MRI, with a focus on vessel imaging, are sufficiently accurate and reliable as a preoperative planning method for PSSS in patients who are not suitable for the TIPS procedure.

VI Materials and methods

VI . I Study design

In order to test the accuracy and reliability of CT and MRI imaging in the planning of PSSS, a retrospective study approach was used to compare the semi-blind evaluation of preoperative images through two radiologists with different work experience and the intraoperative decision taken by our surgeons.

For the evaluation of the images, various parameters such as the diameter and openness of relevant vessels, as well as the distances and interposed structures between them was considered. The individual semi-blinded, clinically oriented evaluation of the technically possible shunt variants and ultimately the decision of which variants would be better suited was conducted. The surgical portosystemic shunt actually being successfully performed was considered as reference.

The working hypothesis was that the clinically-based evaluation of cross-sectional images results in an accurate and reliable preoperative selection of the most suitable shunt procedure.

This study was based on the Helsinki Declaration and the principles of good scientific practice. The study protocol was examined and confirmed by the ethics committee of the Charité - Universitätsmedizin Berlin. Our institutional review board approved the study protocol including adult and pediatric patients, waiving informed consent (application number EA1/148/14) because of the retrospective study design.

VI . II Patient profile

To establish a representative patient group, all patients treated in our surgical department in the period from March 2002 to September 2013 were included retrospectively, fulfilling the following inclusion or exclusion criteria:

- the ICD coding of a portosystemic shunt (5-391.0-2) had to be documented in the patients' files and the above-mentioned interventions had taken place;
- the patients had a CT or MRI imaging examination either in our Radiology Department or were able to provide external images;

- complete documentation of the surgical procedure, intraoperative diagnostics, technical success (documented by postoperative CT-A, MRI-A or Doppler-US) was available;
- patients having a temporary shunt procedure (e.g. as a prehepatectomy bridging procedure) as well as unsuccessful trials or interrupted operations were excluded;
- a comprehensive documentation of the clinical symptoms before surgery was available.

Sixty-five patients who had undergone PSSS between March 2002 and September 2013 were retrospectively identified in the surgical database of our institute.

All patients had been classified as unsuitable for TIPS procedure. The main reason for not choosing TIPS was prehepatic PHT with chronic extrahepatic portal vein occlusion in 31 patients (70%). In 7 pediatric patients with patent portal venous flow, PSSS was preferred due to the still incomplete body growth. In 2 patients, PSSS was indicated because of chronic TIPS occlusion. One patient was treated with PSSS during a hemicolectomy for cecum carcinoma to avoid a further intervention. Another patient was unsuitable for TIPS because of a previously performed right hepatic trisectiorectomy due to a Klatskin tumor. In the other two patients, PSSS was preferred because of vascular anomalies (intrahepatic portal vein dysplasia and a mesenteric arteriovenous malformation).

Databases of the surgical reports, histology reports, laboratory results, images of cross-sectional exams and clinical outcome were obtained. Nineteen of the sixty-five were excluded for having incomplete medical records, or lack of preoperative images, or for having had shunt surgery as a temporary measure prior to hepatic transplant. Two patients underwent an atypical shunt procedure, which was not part of the retrospective imaging-based evaluation and were hence excluded (Figure 2).

The remaining forty-four patients were taken into this study, and had had a preoperative CT (n = 33) and/or MRI examinations (n = 15; n=4 patients with both CT and MRI) with contrast-enhanced vascular presentation. Of these, 19 (43%) were younger than 18 years of age, with three infants (< 2 years), nine children (2 to 12 years) and seven adolescents (12 to 18 years). The mean age in adult patients (n=25) was 44 years. The overall mean patient age was 28 years (range, 0-71). Both genders were equally represented (22 each) in the study population.

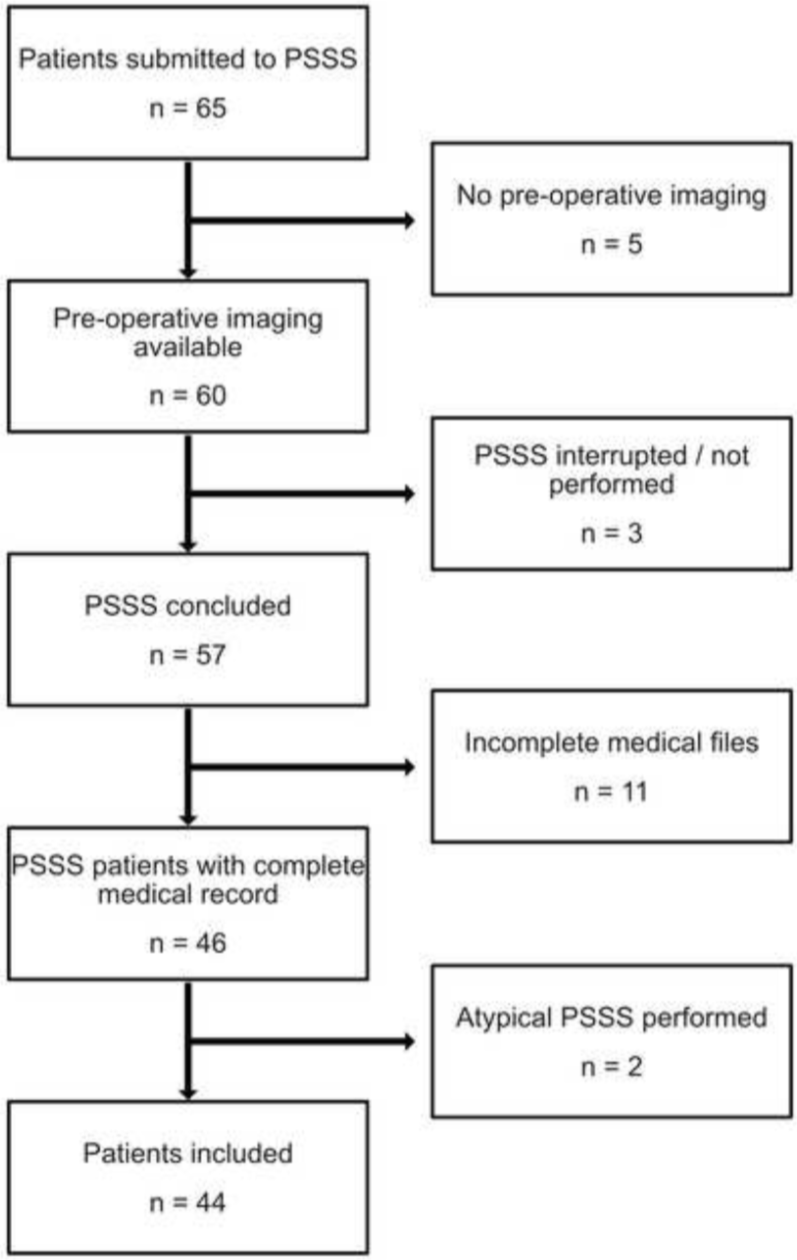

Figure 2. Flow chart of retrospective enrollment (Reprinted with permission from Fehrenbach U, Gül-Klein S, de Sousa Mendes M, *et al.* Portosystemic shunt surgery in the era of TIPS: imaging-based planning of the surgical approach. *Abdom. Radiol.* (2020))

VI . III Surgical procedures

In this study, the following shunting possibilities were considered: end-to-side (ES) and side-to-side (SS) portacaval (PC), ES and SS mesocaval (MC), proximal, distal and SS splenorenal (SR) and mesoportal (Meso-Rex). All patients underwent surgery via laparotomy. The impossibility of performing TIPS was taken as a premise.

Based on an algorithm proposed by our surgical team, considering factors such as age, indication, urgency of vascular decompression, vascular beds to relieve, etc. (Table 2), and with regard to anatomical, radiological and clinical interpretations of each case, the most appropriate shunt variants were recommended by the observers. This algorithm is based mainly on Puhl 2011[39] and takes the physiological properties of each shunt into account. It was used in our retrospective analysis as a guideline, not as an absolute rule, for our recommendation. In two cases, however it was stated as being possible by the radiologists. Different surgical departments have different opinions, and it would not have made sense to draw comparisons with the modus operandi of any department but that of our own.

As summarized below (Table 2), the following shunts, with the corresponding basic indications, are favored by our surgeons: direct ES PC shunt in acute variceal bleeding; MC, distal SR or SR SS in extrahepatic portal vein thrombosis; Meso-Rex in children with extrahepatic portal vein thrombosis (with open intrahepatic portal vein tree); PC or MC SS with or without an interponate at Budd-Chiari; no PC, MC or distal SR in the case of predictable liver transplantation; no Warren, but PC or MC in ascites.

The shunt variants predicted by the radiologist were then compared to the shunts actually performed by the surgeons.

Indication	**Preferred shunt**
acute esophageal bleed	portacaval (EE)
extrahepatic portal thrombosis	mesocaval, splenorenal (distal SS)
extrahepatic portal thrombosis in children	Meso-Rex
Budd-Chiari syndrome	portacaval or mesocaval
ascites	splenorenal (not distal)
possible liver transplantation candidate	portacaval or mesocaval

Table 2. Surgical algorithm

VI . IV Cross-sectional imaging technique

Multiphasic contrast-enhanced (with iopromide [Ultravist 370®, Bayer Schering Pharma] or with iobitridol – [Xenetic 350® - Guerbet GmbH] CT was performed using a 16- or 64-slice scanner (Light Speed Power 16 or VCT 64; GE Medical Solutions, Fairfield, CT) using triple-phase technique with arterial (~15s delay), portal venous (~40s delay) and venous phase (~80s delay). Primary slice thickness was 0.625 mm. Tube voltage was 120 kV, tube current was modulated automatically based on a noise index of 15 and a maximum allowed current of 350 mAs. Maximum intensity projections (MIP) were reconstructed for each contrast phase. The anatomical parameters of interest were measured in the venous phase.

Gadoterate meglumine (Dotarem® - Guerbet GmbH) or gadobutrol (Gadovist® - Bayer Schering Pharma) enhanced MRI was carried out at a 1.5-Tesla system (Siemens Magnetom Avanto, Siemens Healthcare, Erlangen, Germany) with an eight-channel body phased-array surface coil. Anatomical parameters were measured in axial and coronal VIBE post-contrast T1-weighted gradient echo (GE) (Fast Low-Angle Shot (FLASH) sequences with a TR of 120 ms and a TE of 7.47 ms, flip angle 70 °, slice thickness 6 mm, spacing 7 mm, matrix size 255 °ø 340 and in T2-weighted half Fourier-acquired single shot turbo spin echo (HASTE) sequences with a TR of 2 ms and a TE of 87 ms, flip angle 148 °, slice thickness 6 mm, spacing 7 mm, matrix size 255 °ø 340)

Patients with images acquired at other institutions were included in the study if the images were deemed valid for analysis.

VI . V Preoperative image analysis

Preoperative images of all 44 patients, CT (n=33) and/or MRI scans (n=15) with contrast (n=4 patients having had both CT and MRI), were analyzed using a dedicated PACS viewing workstation (Centricity, GE Healthcare, General Electric, Milwaukee, USA) by two radiologists with different levels of experience (Observer 1 (O1; T.D.): 12 years and Observer 2 (O2; J.S.): 4 years of experience in abdominal imaging), blinded to the later chosen surgical procedure, guided by the clinical characteristics of each case.

This evaluation considered anatomy patency and diameter of the portal venous system. Maximal diameters of the possible shunt vessels were measured at the suggested connection (down- and upstream) site by the radiologists. The shortest distances between the possible shunt vessels (inferior vena cava (IVC), portal vein (PV), left and right portal vein branch, superior mesenteric vein (SMV), splenic vein (SV), and left renal vein (RV)) were measured. Interposed structures between possible shunting vessels (requiring tissue resection before connection of the shunt vessels), as well as a possible cavernous transformation of the portal vein[61] (Figure 3) were noted as a factor of complexity. Further factors of complexity included: large vessel distance with necessity of graft interposition (distance >20 mm), thrombosis adjacent to connecting vessels (requiring additional thrombectomy) as well as the unavoidable use of a collateral vein instead of (occluded) major veins for shunt realization. Measurements and identification of factors of complexity were performed by O1. The results were available for both observers in the decision process of which shunt technique was the most adequate.

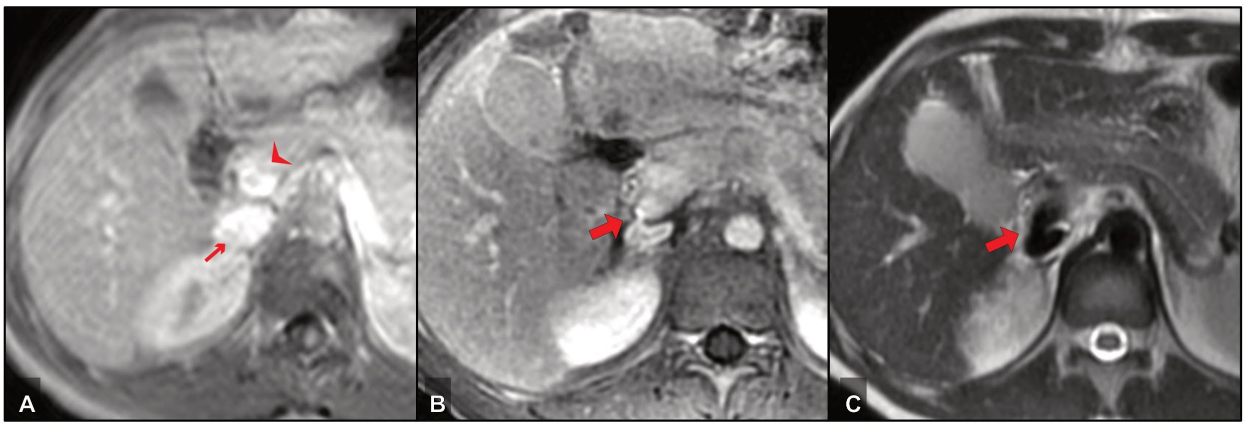

Figure 3: 17-year-old female patient with Wilson's Syndrome and recurrent variceal bleedings – PSS procedure: portacaval side-to-side; **A**: Preoperative MRI, post-contrast T1-w; **B**: Postoperative MRI, post-contrast T1-w; **C**: Postoperative MRI, T2w; Small arrow: IVC, **Arrowhead**: Portal vein, **Bold arrow**: Portacaval anastomosis. (Reprinted with permission from Fehrenbach U, Gül-Klein S, de Sousa Mendes M, *et al.* Portosystemic shunt surgery in the era of TIPS: imaging-based planning of the surgical approach. *Abdom. Radiol.* (2020))

Based on the information available in this retrospective analysis, a ranked recommendation (first and second choice) of two shunt techniques including the appropriate anastomosis was proposed by each of the two observers:

1. Splenorenal
    - Anastomosis: proximal end-to-side (Linton), distal end-to-side (Warren) or side-to-side (Cooley)
2. Portacaval
    - Anastomosis: end-to-side or side-to-side
3. Mesocaval
    - Anastomosis: side-to-side

4. Meso-Rex Shunt

Each observer ranked the two most adequate options and estimated the predictable surgical difficulty based on factors such as the necessity of resection of intercepting structures, graft interposition, or thrombectomy as well as the probable use of a collateral vein instead, for example an occluded major vein for shunt realization. Each proposed technique was further graduated into “standard” or “complex”. If any factor of complexity was present, the procedure was classified as complex.

During the decision process, the two observers were blinded to the later chosen surgical procedure. The recommendations made by the two observers were compared with the shunt procedures that the patients in our analysis actually received.

Therapy success (shunt patency) was evaluated up to discharge after surgery (<30d). Therapy failure was defined as early shunt occlusion or if major complications (re-bleeding; organ failure) occurred or death occurred.

To correlate therapy success to vessel diameters, the shunt vessel ratio was calculated by the formula:

$$diameter_{\text{distal shunt vessel}} / diameter_{\text{proximal shunt vessel}}$$

The shunt vessel ratio, diameter of the smaller shunt vessel and distance of the connected vessels were correlated with PSSS outcome.[62]

VI . VI Statistical analysis

Statistical analysis was performed using SPSS Statistics Version 22 (IBM, Armonk, NY, USA). To evaluate the difference between the accuracy of CT and MRI in preoperative planning, χ^2 test was used. Cohen’s *κ* was used to evaluate interrater reliability. Continuous variables from two independent samples were evaluated using the Mann–Whitney *U* test. P-values <0.05 were considered statistically significant.

A receiver operating characteristic (ROC) curve was used to illustrate the diagnostic ability of a binary classifier system (choice of interposition shunt regarding distance between the anastomosed vessels) and its discrimination threshold. Correlation analysis was performed using Spearman rank correlation.

VII Results

The diagnosis distribution underlying PHT, signs and clinical findings on admission as well as leading indications for surgery are shown in Tables 3, 4 and 5.

The average MELD score (applicable to patients ≥12 years) was 12 (range, 7 to 24). For patients below 12 years of age, the average PELD score was 1.7 (range, 0 to 10.9). In the overall collective, the average serum albumin level was 3.42 g/dl (range, 2.0 to 5.1).[62]

Main causes leading to PHT	**n**	**%**
extrahepatic portal vein thrombosis	31	70%
associated with liver cirrhosis	7	
other causes (e.g. clotting disorder)	24	
liver cirrhosis	16	36%
metabolic / toxic	13	
viral hepatitis	2	
autoimmune hepatitis	1	
Wilson’s disease	1	2%
Rendu-Osler-Weber disease	1	2%
Budd-Chiari syndrome	1	2%
post-hemihepatectomy lymph fistula	1	2%

Table 3. Diagnosis underlying PHT

Signs and clinical findings of PHT	**n**	**%**
esophagogastric varices	40	91%
splenomegaly	31	70%
ascites	19	43%
advanced stage symptoms*	3	7%

Table 4. Signs and clinical findings on presentation
**hepatorenal syndrome, hepatic encephalopathy, spontaneous bacterial peritonitis*

Indication for PSS surgery (complications of PHT)	n	%
esophageal varices	30	66%
varices with previous bleed episode	25	57%
acute variceal bleeding	2	
esophageal varices + hypersplenism	5	11%
splenomegaly and secondary thrombocytopenia	19	43%
excessive ascites	5	11%
intrahepatic arterioportal venous shunts	2	4,3%

Table 5. Main indication for surgery

As for the shunts performed in this study group, Table 6 shows how frequent each of the various shunt options were undertaken.

Shunt	n	%
splenorenal	15	34%
side-to-side (Cooley)	10	
distal (Warren)	3	
proximal (Linton)	2	
portacaval	18	41%
end-to-side	12	
side-to-side	6	
mesocaval	11	25%
side-to-side	11	
Meso-Rex	0	0%

Table 6. Portosystemic shunt performed

18 patients received a portacaval PSSS (Figure 3), in which end-to-side was the most commonly used anastomosis. Splenorenal (Figure 4) and mesocaval (Figure 5) PSSS were

performed 15 and 11 times, respectively. A Meso-Rex shunt was not chosen by the surgeons in our evaluated cases. However, as it was one of the available options to the radiologists reading, it is still mentioned in Table 5. All PSSS procedures included in this study were performed or at least supervised by the same surgeon.

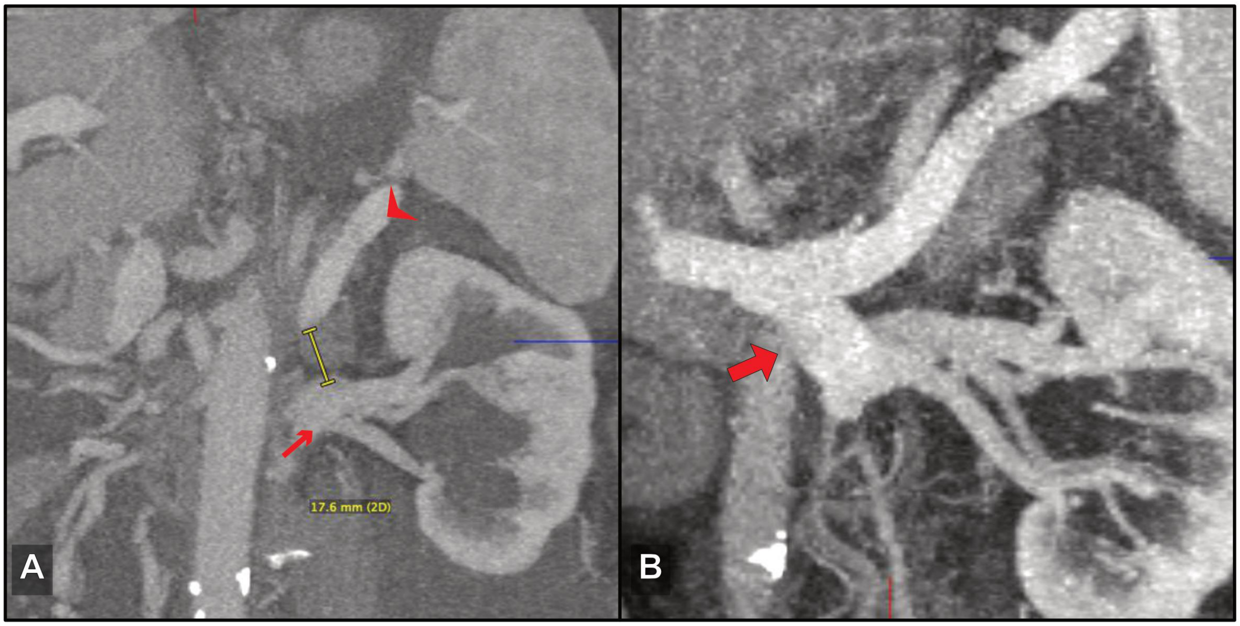

Figure 4: 71-year-old male patient with excessive ascites after extended right hemihepatectomy (diagnosis: intrahepatic cholangiocarcinoma) – PSSS: splenorenal side-to-side; **A**: Preoperative CT, oblique MIP reconstruction; **B**: Postoperative CT, oblique MIP reconstruction; **Small arrow**: Left renal vein, **Arrowhead**: Splenic vein, **Bold arrow**: Splenorenal anastomosis (Reprinted with permission from Fehrenbach U, Gül-Klein S, de Sousa Mendes M, et al. Portosystemic shunt surgery in the era of TIPS: imaging-based planning of the surgical approach. *Abdom. Radiol.* (2020))

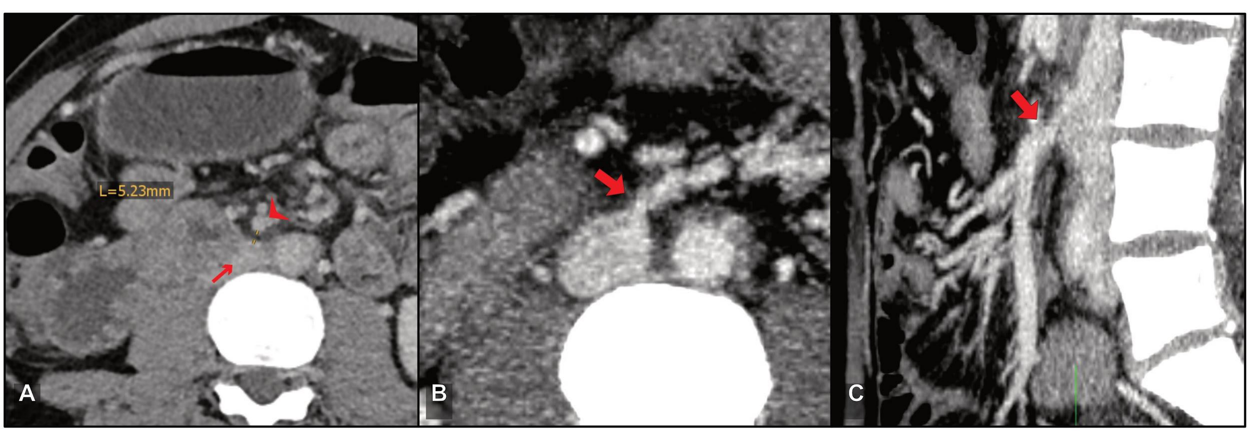

Figure 5: 49-year-old male patient with liver cirrhosis, extrahepatic portal vein thrombosis and advanced symptoms – PSS procedure: mesocaval; **A**: Preoperative CT; **B**: Postoperative CT, axial MIP

reconstruction; **C**: Postoperative CT, sagittal MIP reconstruction; **Small arrow**: IVC, **Arrowhead**: SMV, **Bold arrow**: Mesocaval anastomosis. (Reprinted with permission from Fehrenbach U, Gül-Klein S, de Sousa Mendes M, *et al.* Portosystemic shunt surgery in the era of TIPS: imaging-based planning of the surgical approach. *Abdom. Radiol.* (2020))

When considering the choice of shunt, i.e. of the vessels to be used, the correct combination was ranked by the most experienced observer (O1) and the least experienced observer (O2). The observers' accuracy when suggesting anastomoses, and whether they were correct as a first choice (fair interrater reliability (Cohen's $\kappa = 0.271$, $p = 0.006$) or within the two first choices, is shown in Table 7. Table 8 shows the accuracy of the observers' choices when considering both vessels and the way they should be anastomosed, (e.g. EE, SS, proximal, distal, etc.). Interrater reliability for the first choices of vessels and anastomosis was fair (Cohen's $\kappa = 0.257$, $p < 0.001$). There was no significant difference in the accuracy between MRI or CT evaluation in both observers (p>0.05).[62]

	O1	**O2**
Accuracy of suggested shunts		
1st option		
CT	73%	52%
MRI	80%	60%
p-value	0.728	0.756
1st + 2nd option		
CT	88%	76%
MRI	100%	73%
p-value	0.294	1.000

Table 7. Accuracy in predicting vessels involved in shunt procedure

Accuracy of suggested anastomotic variants	O1	O2
1st option		
CT	64%	36%
MRI	53%	33%
p-value	0.538	1.000
1st + 2nd option		
CT	79%	67%
MRI	73%	60%
p-value	0.720	0.749

Table 8. Accuracy in predicting shunt procedure and anastomotic variants

The surgeons chose a vessel connection which was not included in the first two choices of O1 in 5 cases (11%) and of O2 in 12 cases (26%).

In 15 patients, the surgeon chose a PSSS technique that was classified as complex by the radiologist. Complexity of procedure was confirmed by the operative report in 13 (87%) of these patients. The radiological assessment showed a sensitivity of 80% and specificity of 96% in the prediction of a complex surgical procedure. In two patients, a resection of interposing structures was deemed necessary by the radiologists. In one case, a subsegmental liver resection (caudate lobe) was performed (Figure 6 A). In the second case, embolization of an interposing arteriovenous malformation was performed in preparation for the PSSS surgery. A third patient also received a subsegmental (caudate lobe) liver resection, which was not suggested by the radiology observers. Partial thrombosis of the connecting vessels was identified by the radiologists in four patients and thrombectomy was performed in three (75%) of these patients during the surgical procedure (Figure 6 B). The necessity of using a collateral vessel was proposed and performed in one patient (100%; adrenal vein). In nine patients, the distance between the connecting vessels was >20 mm and use of a graft interposition was proposed by the observers. Eight (89%) of these patients received a graft (Figure 6 C & D).[62]

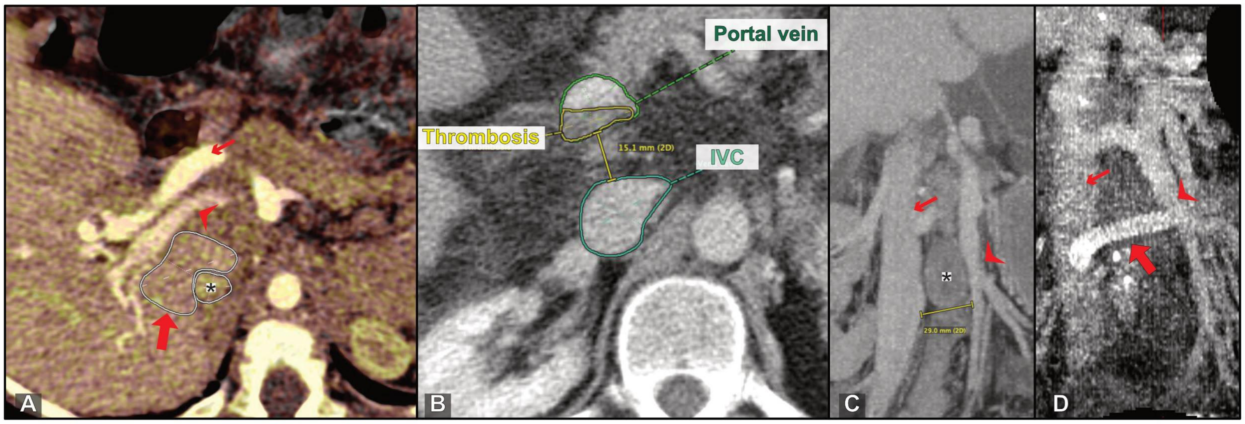

Figure 6: Factors of complexity; **A**: Oblique axial CT (fused portalvenous phase and venous phase) shows an interposing caudate lobe (PSS procedure: portacaval end-to-side with subsegmental liver resection); bold arrow: caudate, arrowhead: portal vein, small arrow: hepatic artery, asterisk: IVC. **B**: Axial CT with a partial thrombosis of the extrahepatic portal vein (PSS procedure: portacaval side-to-side after thrombectomy); **C**: Oblique coronal CT MIP shows a large distance between IVC (small arrow) and SMV (arrowhead) of 29 mm. This patient received a graft interposition (allograft), which is seen in D (PSS procedure: mesocaval with the use of a graft interposition); **D**: Postoperative, oblique coronal CT MIP reconstruction shows the graft interposition (bold arrow) that connects SMV (arrowhead) and IVC (small arrow). (Reprinted with permission from Fehrenbach U, Gül-Klein S, de Sousa Mendes M, et al. Portosystemic shunt surgery in the era of TIPS: imaging-based planning of the surgical approach. *Abdom. Radiol.* (2020))

In one case, the least experienced observer had excluded a shunt chosen by the surgeons. It was, however, a collateral vessel of the portal vein, itself occluded, in a so-called portacaval shunt. The most experienced observer ranked this option as first of the three possible options and as highly surgically demanding. In none of the remaining cases did the observers exclude a shunt that ended up being the one performed.

In the entire collective, 10 patients received a graft interposition (splenorenal n=3; portacaval n=2; mesocaval n=5). A ROC analysis of vessel distances and the use of a graft was performed and showed an AUC of 0.950 ($p<0.001$) (Figure 7). According to the Youden index, the optimal cut-off value was 20 mm (Youden index: 0.771). In our cohort, only one patient with a distance of >20 mm did not receive a graft interposition, and later this patient developed early shunt occlusion.

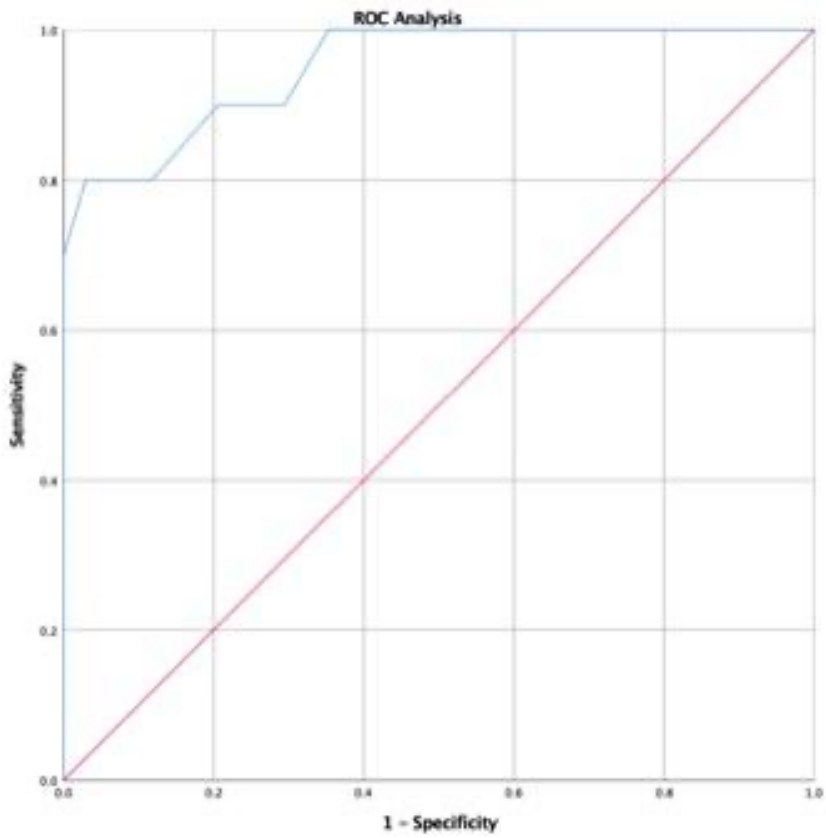

Figure 7. ROC analysis – distance of connected vessels and need of graft interposition, AUC: 0.950 (p<0.001), max. Youden index: 0.771 at 20 mm. (Reprinted with permission from Fehrenbach U, Gül-Klein S, de Sousa Mendes M, et al. Portosystemic shunt surgery in the era of TIPS: imaging-based planning of the surgical approach. *Abdom. Radiol.* (2020))

In the entire collective, eight patients (18%) showed an early shunt failure / occlusion (<30d after shunt surgery). Three of these patients (shunt indication: acute variceal bleeding) died during hospitalization. Therapy success was achieved in the remaining 38 patients (82%) and their shunts were perfused until discharge.

We analyzed the cases in which the surgeon chose a vessel connection not recommended by the experienced O1 (n=5). Two out of these five patients (40%) died during their hospitalization.

Analysis of the therapy success showed a significant correlation between shunt vessel distance and early occlusion. The larger the distance, the higher the chance of early shunt occlusion (p=0.030). There was no significant correlation between the vessel size of the smaller connecting vessel or the shunt vessel ratio to early shunt occlusion (p>0.05) (Table 9).

Outcome of shunt patency (<30 days)							
	Success (n=36)			Failure (n=8)			Significance
	Mean	SD	Range	Mean	SD	Range	
Distance between vessels (mm)	12.67	11.69	56.00	20.38	10.87	33.00	p = 0.030
Small shunt vessel diameter (mm)	10.17	4.39	21.00	10.25	3.01	9.00	p = 0.709
Shunt vessel ratio	0.734	0.567	2.742	0.500	0.156	0.475	p = 0.482

Table 9. Correlation analysis between shunt vessel diameter and distance and early shunt occlusion (<30d). (Reprinted with permission from Fehrenbach U, Gül-Klein S, de Sousa Mendes M, et al. Portosystemic shunt surgery in the era of TIPS: imaging-based planning of the surgical approach. *Abdom. Radiol.* (2020))

VIII Discussion

Despite the successful implementation of TIPS, PSSS also has benefits in the treatment of advanced PHT.[63] We retrospectively identified 44 patients who underwent PSSS at our center, in which TIPS was not considered to be an adequate treatment option. As long-term results of different shunting techniques are comparable, preoperative workout should focus on anatomical prerequisites.[44] This is why this study focused on the impact of preoperative radiological forecast. Our analysis was able to show that imaging-based planning of the procedure and identification of complicating circumstances are adequate in contrast-enhanced CT and MRI. We could also show that an experienced radiologist and a multidisciplinary discussion to choose the most appropriate surgical management should take place to tackle the complex imaging findings and the consecutive planning of the surgical approach.

Increased periprocedural morbidity rates of PSSS due to advanced liver failure requires adequate planning to avoid extensive surgical exploration.[64] Reliable imaging-based procedure planning of the portal venous anatomy has been shown in patients undergoing liver transplantation and pancreatic surgery.[65,66] Precise puncture guidance in TIPS procedure is possible with contrast-enhanced CT and the possibility of 3D reconstructions.[49,67] However, as there is no existing data on whether imaging-based procedure planning is adequate in PSSS, our study aimed at tackling this knowledge gap.

We were able to show that the experienced reader could predict which shunt technique was going to be used with high accuracy in both CT (88%) and MRI (100%). The accuracy of the not so experienced reader was lower (with about 75% in both modalities). The fair interrater reliability of their first choices underlines the need for an experienced radiologist in the interpretation of the complex preoperative imaging.[62]

There were no significant differences in the preoperative accuracy of MRI and CT in both readers. These findings support the already shown high impact of CT venography in the evaluation of portosystemic collateral vessels.[68] In 10% of the patients, the surgeon chose a vessel connection which was not recommended by the experienced reader. Deviation from preoperative imaging findings and recommendations might lead to higher rates of therapy failure and worse patient outcome, as shown by the high incidence of shunt failure / mortality (40%) in such cases amongst our patients. Comparably, it has been shown that intraoperative management of portosystemic shunts during liver transplantation is improved by preoperative CT assessment.[69-]

We conclude that besides vessel location, MRI and CT studies are suitable to identify complicating factors that require additional surgical techniques for example a caudate lobe enlargement, frequently found in patients with PHT requiring PSSS.[70] Therefore, interception of a hypertrophied caudate lobe has to be considered in the planning of a portacaval shunt surgery. Our study shows that adequate imaging-based preoperative planning can be achieved with reliable identification of interfering structures and large distances between connecting vessels that may require the use of interposition grafts. However, there are no defined standards for which distance the use of a graft interposition is recommended. In our analysis, we were able to identify a 20 mm vessel distance as an optimal cut-off value for an interposition graft in our context. Besides the use of grafts, the vessel distance was the only identified risk factor of early shunt failure / occlusion in our cohort. The diameters of the connected vessels showed no correlation to the occurrence of early shunt occlusion. The incidence of therapy failure / shunt occlusion (17%) observed in our cohort was the result of the broad variety of shunt indications with a high percentage of advanced and acute cases with poor hepatic reserve, compared to other studies.[62,71,72]

An additional useful method that could have been considered for both preoperative anatomical and postoperative patency evaluation is computer tomographic portograph. Which is based on portal enhancement of the liver by infusion of contrast material through the superior mesenteric artery and the celiac trunk for evaluating the portal venous system and its dominant drainage route in the case of portal hypertension.[73] This, however, was not being performed at our institute during the time frame of this study.

As limitations to the study, we point out its retrospective study design and its inherent surgical bias due to the surgical preferences and expertise of the attending surgeons (e.g. in no case was a Meso-Rex shunt performed even though it has been recently shown that this is a very good option for younger patients[57-59]). Our surgeons were also aware of the preoperative imaging findings; however, there was no documentation on how the imaging findings influenced the surgeons' decision of which procedure to choose. Overall, the PSSS technique chosen might also have been influenced by the individual experience of the surgeon, which might also have changed over the evaluated period of eleven years. The more experienced radiologist could have been better at predicting because he knew the surgeons and their preferred techniques more intimately. To minimize these effects, we evaluated the first two radiological choices instead of using only a single recommendation. Nonetheless, practice patterns and surgeons' experience can be variable between institutions, so that the results of our study may not be applicable to other sites. Our results could pave the way for a prospective study, which is needed to answer the question if presurgical imaging provides adequate and important information and influences patient outcomes.

We show that in the interdisciplinary planning of PSSS, preoperative evaluation through both CT and MR venous angiogram is of great importance, as is the integrative view over anatomy, clinical presentation and knowledge of the surgical techniques by the radiologists. The difference between the results achieved with CT and MRI are not significant. This lies probably on the minute number of patients who had a preoperative MRI.

Attempting to establish the perioperative patency rate as a clinical outcome, as well as its relevance to the aim of this study, also presented difficulties. We only considered the patency up to discharge for lack of complete follow-up data (as many patients were lost to follow-up). Long-term patency is multifactorial and not only a consequence of the vessels chosen, hence the lack of relevance to this study. Isolate sampling of the postoperative paths based on documentation has also shown errors of misinterpretation reporting contrary to the radiological findings, hence making some of the documented information of questionable reliability.

With its minimally invasive quality, and in being easily revised in the case of loss of both function and patency, TIPS introduced a new era in the management of PHT. It is, however, suboptimal in certain cases, such as extrahepatic thrombosis because it cannot bridge the obstructed segments, as well as advanced hepatic cirrhosis because it may induce hepatic encephalopathy (if regarded physiologically, it offers a unique unselective (portacaval) shunting possibility). In a pediatric context, the use of Meso-Rex has also recently been given support for being a physiological and anatomical bypass procedure for relief of extrahepatic portal vein obstruction while simultaneously restoring mesenteric venous return to the liver.[74]

TIPS as a nonsurgical modality also precludes the possibility of simultaneous splenectomy and radical devascularisation.[24]

In comparison, portosystemic shunts, within their its aforementioned variability and in allowing a vaster intraabdominal vascular intervention, do present as a proper modality in certain cases.[74] They also require proper preoperative planning, and that was the focus of this study as there is no literature in this regard.

In conclusion, preoperative cross-sectional imaging and the interpretation by an experienced radiologist can be of guidance to the surgical team in PSSS, achieving accurate planning and reliable exclusion of unfavorable shunt variants. CT and MRI examinations can provide technical feasible alternatives and identify complicating factors (as use of interposition graft, resection of interposing structures or the need for thrombectomy). Hence, we propose preoperative assessment of the technical feasibility of various shunting techniques based on vascular anatomy as a surgical prerequisite.

This study also alerts to the need of further prospective research comparing CT and MR angiograms especially in younger patients, since in this group the lack of need of radiation would be of great value.

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X Statement of responsibility / Eidesstattliche Versicherung

Ich, Miguel de Sousa Mendes, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: “Imaging-based Planning of Portosystemic Shunt Surgery” selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.org) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.

Datum Unterschrift

XI Declaration of contributions to co-authored publications / Anteilserklärung an etwaigen erfolgten Publikationen

Teile der Monographie bereits publiziert worden. Vom Verlag bestehen keine Einwände Teile des in unserem Artikel (DOI: 10.1007/s00261-020-02599-z) vorliegenden Datensatzes in dieser Dissertation zu verwenden. Diese sind deutlich zitiert.

Der Promovend hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Fehrenbach U, Gül-Klein S, **de Sousa Mendes M**, Steffen I, Stern J, Geisel D, Puhl G, Denecke T. Portosystemic shunt surgery in the era of TIPS: Imaging-based planning of the surgical approach. Abdominal Imaging (2020)

Beitrag im Einzelnen: substanzielle Beiträge zur Ausgestaltung des Konzepts der Arbeit unter Anleitung von Herrn Prof. Dr. Denecke, Erstellung der Kohorte aus den Klinikdatenbanken mit Unterstützung und Betreuung durch Frau Dr. Gül-Klein und Frau Dr. Stern, Pseudonymisierung der Bilddatensätze und Erstellung der Erfassungsbögen, Datenmanagement (aus seiner statistischen Auswertung sind die Tabellen 1 bis 8 entstanden) und Zuarbeit bei der verblindeten qualitativen Bildanalyse durch die beiden erfahrenen Observer, selbständige quantitative Bilddatenanalyse nach Einarbeitung durch Frau Dr. Stern und unter Kontrolle von Herrn Dr. Fehrenbach, assistierte Interpretation der Daten, Entwurf der Publikation, Überarbeitung des Artikels mit den Erst- und Koautoren um wichtigen intellektuellen Inhalt zu verbessern, Erstellung der Abbildungen sowie Überarbeitung dieser mit Herrn Fehrenbach und schließlich Prüfung der Druckfahne.

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Unterschrift, Datum und Stempel des/ erstbetreuenden Hochschullehrers

____

Unterschrift des Doktoranden

XII Curriculum vitae

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection.

XIII Complete list of publications

Fehrenbach U, Gül-Klein S, **de Sousa Mendes M**, Steffen I, Stern J, Geisel D, Puhl G, Denecke T. Portosystemic shunt surgery in the era of TIPS: Imaging-based planning of the surgical approach. Abdominal Radiology (in press)

Puppe J, Dieterich M, Bayer C, Neiman J, **de Sousa Mendes M**, Gaß P, Lermann J, Schott S. Senology in Gynaecology Specialist Training: a Baseline Survey from 2014. Geburtshilfe Frauenheilkd. 2016 May;76(5):564-569.

Vasconcelos I, **de Sousa Mendes M**, Linke J, Schoenegg W. Sudden onset diffuse erythema and oedema of the breast. BMJ. 2015 Aug 6;351

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