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Hepatic Hypertrophy in Normal and Cirrhotic Livers Following Portal Vein Embolization: Comparative Assessment of 2 Different Embolic Regimens in a Large Animal Model

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“It always seems impossible

until it’s done”

Nelson Mandela

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Zusammenfassung

Patienten mit Lebermetastasen und HCC-Patienten erfüllen häufig nicht die Einschlusskriterien für eine kurative Resektion, so dass ihnen meist nur eine Zweit- oder Drittlinienbehandlung bleibt, die ihre Lebenserwartung nur um Monate verlängert (Van Cutsem et al., 2016, Rocha and Helton, 2012). Seit Jahren gibt es zahlreiche Veröffentlichungen über die optimale Methode zur präoperativen Leberregenerationsinduktion. Zu den beiden bekanntesten Methoden gehören *Associating Liver Partition with Portal vein ligation for Staged hepatectomy* (ALPPS) und die *Portalvenenembolisation* (PVE) (Schnitzbauer et al., 2012, Kinoshita et al., 1986). Während ALPPS nachweislich mit einem größeren Restlebervolumen (FLR)-Anstieg verbunden ist, hat sich PVE als die sicherere Therapieoption für Patienten herausgestellt (Isfordink et al., 2017, Moris et al., 2018). Daher hat sich PVE in den letzten Jahren weltweit als Standardbehandlung für diese Patienten durchgesetzt. In der klinischen Praxis werden häufig verschiedene Embolisationsmittel eingesetzt, darunter NBCA und Microspheres (mit oder ohne Coils). Insbesondere bei Patienten mit eingeschränkter Leberfunktion aufgrund einer großen Tumorlast oder einer zirrhotischen Leber ist eine rasche Erhöhung der FLR für die anschließende Resektion erforderlich. Diese Patienten waren in zuvor veröffentlichten Studien unterrepräsentiert und es lassen somit keine klaren Schlussfolgerungen ziehen. Daher wurde in dieser Arbeit mit einem tierexperimentellen Ansatz untersucht, ob es ein bevorzugtes Embolisationsmittel für diese Patientengruppe gibt.

Zu diesem Zweck habe ich in Yale, USA, ein Großtiermodell für Leberzirrhose eigenständig etabliert (Avritscher et al., 2011). Unser Labor hatte bis zu diesem Zeitpunkt noch nicht mit Schweinen gearbeitet. Daher wurde das gesamte Projekt von mir selbständig aufgebaut und geleitet. Das Tiermodell induziert eine Zirrhose, indem ein Ethanol-ethiodiertes Ölgemisch injiziert wird, das zu einer akuten Leberschädigung und einer langfristigen Verklebung der Sinusoidalstrukturen führt, was nach vier Wochen zu einer bioptisch gesicherten Zirrhose führt. Die PVE wurde dann entweder mit NBCA oder mit Microsphären und Coils in einer normalen oder zirrhotischen Leber durchgeführt. CT-Untersuchungen wurden zu Anfang, zwei und vier Wochen nach der PVE durchgeführt. Nach vier Wochen wurde die Leber entnommen und eine Immunfluoreszenzquantifizierung für CD3, CD16, Ki-67 und Caspase-3 durchgeführt, um die Immunzellinfiltration, die Proliferation der Hepatozyten und die Apoptoseraten zu bewerten.

Das Restlebervolumen stieg in der nicht-zirrhotischen Gruppe im Vergleich zur zirrhotischen Gruppe um etwa das Doppelte an, unabhängig vom verwendeten Embolisationsmittel (18,82% vs. 10,93%, $p<0.01$). Beim Vergleich der Hypertrophiekinetik für beide Embolisate konnte gezeigt werden, dass sich bei Einsatz von Microsphären und Coils das Restlebervolumen in den ersten zwei Wochen am stärksten steigern lies. Im Gegensatz dazu nahmen die mit NBCA behandelten Lebern in ihrem Volumen hauptsächlich zwischen Woche zwei und vier zu. Diese Beobachtung war sowohl bei zirrhotischen, als auch bei normalen Lebern konsistent.

Im Vergleich zu früheren Studien, die NBCA als Embolisationsmittel der Wahl präferierten und die ausreichende Fähigkeit der PVE bei Leberzirrhose in Frage stellten, widerspricht diese Studie früheren Ergebnissen und stellt die Wahl der Embolisationsmittel in Frage. Vor allem Patienten mit eingeschränkter Leberfunktion, die eine schnelle Behandlung benötigen, könnten von diesen Ergebnissen profitieren. Des Weiteren sollte erwähnt werden, dass bisher keine Studie zum Vergleich von Embolisationsmitteln bei PVE ein unterschiedliches klinisches Outcome zeigen konnte und in diesen Studien zirrhotische Patienten zumeist unterrepräsentiert waren (10% aller Patienten,(van Lienden et al., 2013).

Zusammenfassend lässt sich sagen, dass auf der Grundlage der Daten dieser Studie bei Patienten in Hochrisikosituationen mit kritischer Leberfunktion, bei denen eine kurative Resektion in kürzerer Zeit erforderlich ist, Microsphären und Coils statt NBCA gewählt werden sollten. Diese Ergebnisse waren sowohl für normale als auch für zirrhotische Lebern konsistent. Darüber hinaus sollte bei Patienten, die mit Microsphären und Coils behandelt werden ein kürzerer Nachuntersuchungszeitpunkt von zwei Wochen nach der PVE in Betracht gezogen werden.

Summary

Patients with liver metastases and hepatocellular cancer (HCC) patients often do not achieve the inclusion criteria for curative resection, leaving them with secondary or third-line treatment, only increasing their life expectancies by months (Van Cutsem et al., 2016, Rocha and Helton, 2012). For years, numerous publications have been published concerning the ideal way to increase the future liver remnant (FLR) before resection and increase the cohort for curative treatment. The two most known methods include *Associating Liver Partition with Portal vein ligation for Staged hepatectomy* (ALPPS) and *Portal Vein Embolization* (PVE) (Schnitzbauer et al., 2012, Kinoshita et al., 1986). Whereas ALPPS was shown to be associated with greater FLR increase, PVE's have been proven to be the safer option to patients (Isfordink et al., 2017, Moris et al., 2018). Therefore, in recent years, PVE has become the worldwide standard of care. Several embolic agents are commonly used in clinical practice, including n-Butyl cyanoacrylate (NBCA) and microspheres (with or without coils). Especially in patients with impaired liver function by large tumor load or cirrhotic underlying liver, rapid FLR increase is needed for following resection. These patients were underrepresented in previously published studies and, therefore, decision making was challenging. Hence, this study investigated whether this patient group has a preferred embolization agent.

To do so, I independently established a large animal model for liver cirrhosis at Yale, USA (Avritscher et al., 2011). Our laboratory had not yet worked with pigs before. I, therefore, set up and managed the entire project independently. The animal model induces cirrhosis by infusing an ethanol-ethiodized oil mixture that leads to acute liver impairment and long-term clotting of the sinusoidal structures, resulting in biopsy-confirmed cirrhosis after four weeks. PVE was then performed with either NBCA or microspheres and coils in normal or cirrhotic underlying liver. CT scans were performed at baseline, two and four weeks post-PVE. After four weeks, the liver was harvested, and immunofluorescence quantification for CD3, CD16, Ki-67, and Caspase-3 was conducted to assess immune-cell infiltration, hepatocyte proliferation, and apoptosis rates.

The FLR% increased by about twice the amount in the non-cirrhotic vs. cirrhotic group despite the embolic agent used (18.82% vs. 10.93%, $p<0.01$). When comparing the hypertrophy kinetics for both embolic agents, it could be shown that livers treated with microspheres and coils mainly increased their sFLR% in the first two weeks. In contrast, livers treated with NBCA increased their volume mainly between two and four weeks post-PVE. This observation was consistent for both cirrhotic and normal underlying livers.

Compared to previous studies, which suggested NBCA as the choice of embolic agent and questioned the sufficient ability of PVE in cirrhosis, this study contradicts earlier results and questions the choice of embolic agents. In particular, patients with impaired liver function who are in need of rapid treatment could benefit from these results. Furthermore, it should be mentioned that no study comparing embolic agents to date has been able to show a different clinical outcome based on the embolic agent used, and cirrhotic patients were mostly underrepresented in those studies (10% of all patients,(van Lienden et al., 2013).

To conclude, this work provides evidence on the controversial topic of choosing embolic agents in PVE. Based on the data of this study, patients in high-risk situations with critical liver function and those requiring curative resection within a short period of time, microspheres and coils should be chosen rather than NBCA. These findings were consistent for both normal and cirrhotic underlying livers. In addition, a shorter follow-up imaging time point of two weeks post-PVE should be considered for patients treated with microspheres and coils.

List of abbreviations

ALPPS	Associating Liver Partition With Portal Vein Ligation For Staged Hepatectomy
BCLC	Barcelona Clinic Liver Cancer
CCC	Cholangiocarcinoma
CRC	Colorectal Cancer
eLVD	Extended Liver Venous Deprivation
ESMO	European Society For Medical Oncology
FLR	Future Liver Remnant
FNH	Focal Nodular Hyperplasia
HBV	Hepatitis B
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C
HSC	Hematopoietic Stem Cell
HVE	Hepatic Vein Embolization
ICG	Indocyanine Green
KGR	Kinetic Growth Rate
LVD	Liver Venous Deprivation
MRI	Magnetic Resonance Imaging
MWA	Microwave Ablation
NAFLD	Non-Alcoholic Fatty Liver Disease
NBCA	N-Butyl Cyanoacrylate
OS	Overall Survival
PBC	Primary Biliary Cirrhosis
PSC	Primary Sclerosing Cholangitis
PVA	Polyvinyl Alcohol Particles
PVE	Portal Vein Embolization
PVL	Portal Vein Ligation
RFA	Radiofrequency Ablation
SPECT	Single-Photon Emission Computed Tomography
TACE	Transcatheter Arterial Chemoembolization
TAE	Trans-Arterial Embolization
TARE	Transarterial Radioembolization
TELV	Total Liver Volume Estimation

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Introduction

Liver Lesions & Cirrhosis

Lesions in the liver are widespread in the general population. A study found that 28.5% of the population had at least one small focal liver lesion on magnetic resonance imaging (MRI) (Kreft et al., 2001). Only more than half of these lesions are benign (57.3%), the rest is not (42.7%). Especially in patients with known chronic liver diseases like Hepatitis C (HCV), Hepatitis B (HBV), or chronic alcoholism, malignancies are much more common. Besides, patients with a diagnosis of cancer, especially colorectal cancer, are at risk for liver metastases. The Global Cancer Statistics 2020 have shown that cancer in the liver is the second most common cause of cancer-related death worldwide, with over 830.000 deaths per year (Sung et al., 2021).

Benign Lesions

Benign focal liver lesions can be found frequently in patients. A study analyzing 45.319 patients who underwent ultrasound investigation between 2003 and 2013 found that about 15.1% presented with at least one lesion of interest. The most common ones were focal fatty sparing (6.3%), followed by hepatic cysts (5.8%), hepatic hemangioma (3.3%), focal nodular hyperplasia (FNH) (0.2%), and hepatic adenoma (0.04%) (Kaltenbach et al., 2016). Focal fatty sparing of the liver is commonly found in underlying diffuse hepatic steatosis and presented as a hypo or isoechoic lesion on ultrasound. Hepatic cysts are generally asymptomatic fluid-filled cavities. They are more prevalent in the female population, and their etiology can range from infections to benign to malignant origin. It is essential to differentiate between simple cysts, mostly congenital asymptomatic cysts, from complex cysts that demand further treatment (Mavilia et al., 2018). Hepatic hemangiomas are mostly incidentally discovered during abdominal ultrasound. They are primarily asymptomatic blood-filled cavities demanding no further treatment. Only giant liver hemangioma can develop symptoms demanding closer follow-up imaging and sometimes even surgical treatment because of their risk of bleeding (Bajenaru et al., 2015). FNH are benign lesions mostly found in female patients and may be associated with estrogen-based contraception. They are mostly asymptomatic, have no malignant potential, and rarely require further treatment (Hsee et al., 2005). Hepatic adenoma is rarely observed in clinical practice, but because of its risk of bleeding and malignant transformation it needs to be diagnosed and treated (Grazioli et al., 2001).

Malignant Lesions

Malignant liver lesions may appear as primary of secondary liver tumors. They are frequently associated with chronic underlying liver disease such as cirrhosis (primary tumors) or are part of metastatic disease of tumors of different origin (secondary tumors).

The most common malignant liver lesions are liver metastases, followed by hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCC). A recent study analyzing histology samples of 23.154 patients showed that liver metastases were primarily from colorectal cancer (CRC) (34.6%), followed by

pancreatic (7.6%) and breast cancer (6.1%) (de Ridder et al., 2016). In about 10-20% of patients with CRC, synchronous liver metastases occur, and up to 50% will develop them over time (Martin et al., 2020). When comparing patients with liver metastases against non-metastatic CRC, their one-year survival drops from 24% to 15.1% (Horn et al., 2020).

HCC is closely associated with patient cirrhotic underlying liver. Studies showed that about 80-90% of patients with HCC present with cirrhosis (Simonetti et al., 1991). Only 10-20% are non-cirrhotic related HCCs. When separating cirrhotic HCC patients by their presumptive etiology, HCV infection accounted for most cases (27-73%), followed by HBV (12-55%), alcoholism (4-38%), and hemochromatosis (2-6%). Patients with HCC but without cirrhosis, HCV was present in 3-54% of the patients, followed by HBV (4-29%) and alcoholism (0-28%) (Trevisani et al., 1995, Stroffolini et al., 1998, Van Roey et al., 2000, Bralet et al., 2000, Chiesa et al., 2000). A recent study showed that the median overall survival (OS) of HCC patients increased from 6 to 12 months, comparing 1998-2002 to 2008-2016, but remained low (De Toni et al., 2020).

Cholangiocarcinoma has been reported to make up less than 3% of all gastrointestinal tumors and can be classified into intrahepatic, perihilar, and distal based on their location (Kirstein and Vogel, 2016). Risk factors vary based on the country of origin, whereas infections, especially with trematodes, are the most common cause in developing countries, primary sclerosing cholangitis (PSC) is the most common cause in the western hemisphere (Brindley et al., 2021). Mortality of Patients with CCC after one year has decreased, but 5-year survival is still at 10% (Everhart and Ruhl, 2009).

Cirrhosis

Cirrhosis is one of the most significant healthcare system burdens worldwide. It accounts for more than 1 million deaths per year and is the 11th most common cause of death worldwide (Asrani et al., 2019). It is the major risk factor for hepatocellular carcinoma development, the third most common type of cancer worldwide (Villanueva, 2019). Cirrhosis is caused by various chronic liver diseases like alcoholism, viral infection, lifestyle (e.g., non-alcoholic fatty liver disease [NAFLD]), genetic disease (e.g., hemochromatosis, Wilson's disease), primary biliary cirrhosis (PBC) / PSC, and autoimmune-related hepatitis (Schuppan and Afdhal, 2008). NAFLD has become the leading cause of cirrhosis in developed countries due to increased obesity rates, leading to its prevalence of as high as 30% in the US (Younossi et al., 2020). Cirrhosis, therefore, is a multifactorial disease caused by a variety of chronic underlying diseases.

Treatment Options

Colorectal Cancer & Liver Metastases

In about 10-20% of patients with CRC, synchronous liver metastases occur, and up to 50% will develop them over time (Martin et al., 2020). Over the past decade, several approaches have been published on how to treat liver metastases, resulting in the European Society for Medical Oncology (ESMO) consensus guidelines (Van Cutsem et al., 2016). Therapy decisions will be taken in an interdisciplinary tumor board, increasing patients' 5-year survival rates from 15.7% (2004-2006) to 26% (2013-2015) (Zeineddine et al., 2023).

First-line Treatment Of Liver Metastases

The main goal is to maximize the reduction of tumor burden based on the patient's overall clinical condition. The first-line treatment is curative resection, either with/or without chemotherapy, based on the patient's resectability and overall clinical condition. In general, resection can be performed as long as at least two contiguous liver segments remain and adequate blood flow and biliary drainage are guaranteed (Charnsangavej et al., 2006).

Therapy Strategies For Non-Resectable Liver Metastases

A recent study has reported that up to 80% of patients fail to achieve inclusion criteria for curative resection at the point of diagnosis (Engstrand et al., 2018). At present, there are several second or bridging treatments, including neoadjuvant chemotherapy for downstaging, several ablation techniques with or without resection, two-stage hepatectomy, portal vein embolization, or trans-arterial Y-90 radioembolization (Fiorentini et al., 2017).

Neoadjuvant Chemotherapy

Several chemotherapy regimens have been published, with FOLFOX (Folinic acid, fluorouracil, and oxaliplatin) (40.5%) being the most common one, often in combination with bevacizumab, followed by FOLFIRI (Folinic acid, fluorouracil and irinotecan) (25.7%) (Hess et al., 2010).

Ablation Techniques

Radiofrequency ablation (RFA) and microwave ablation (MWA) are currently recommended as curative treatment options for unresectable liver metastases ranging from 0-3 cm (Meijerink et al., 2018).

Two-Stage Hepatectomy

Various two-stage hepatectomy techniques have been proposed. Commonly, patients undergo neoadjuvant chemotherapy, followed by resection of left lobe liver metastases, portal vein embolization, and then resection of right lobe metastases (Dhir and Sasson, 2016). Portal vein embolization is recommended in patients with insufficient future liver remnant volume. By embolizing the vascular structure to the tumor-diseased liver segments and, therefore, redirecting it to the non-diseased lobe,

functional liver parenchyma can be increased and, therefore, following resection made feasible (Kinoshita et al., 1986).

Y-90 Radioembolization

Y-90 radioembolization delivers trans arterially y-90 loaded microspheres directly to the tumor of choice. It is currently indicated for patients with unresectable liver metastases to improve their quality of life and overall survival (Tong et al., 2016).

Hepatocellular Carcinoma

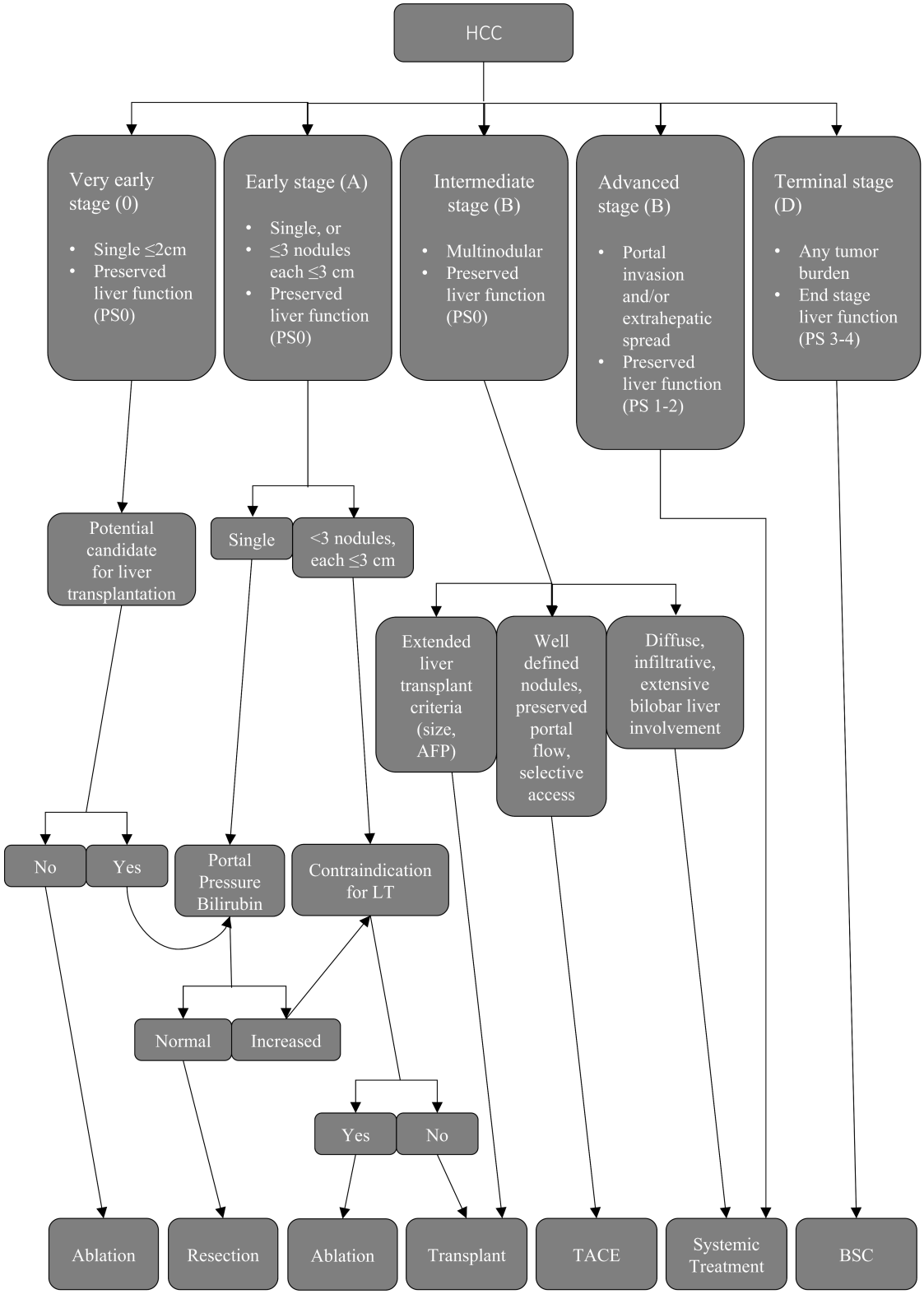

Fig. 1 Barcelona Clinic Liver Cancer (BCLC) staging system (Update 2022)

Barcelona Clinic Liver Cancer (BCLC) staging, including strategies for treatment of hepatocellular carcinoma (HCC). LT = Liver Transplantation, AFP = alpha-Fetoprotein, TACE = Transarterial Chemoembolization, BSC = Best Supportive Care. This figure was published in the Journal of Hepatology, Vol number 76, Reig, Maria et al., BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update, Page No 683, Copyright Elsevier (2021).

HCC is closely associated with a cirrhotic underlying liver. Studies showed that about 80-90% of patients with HCC present with cirrhosis (Simonetti et al., 1991). The treatment of HCC patients is chosen based on their Barcelona Clinic Liver Cancer (BCLC) stage, which ranges from very early stage (0) to terminal stage (D) (Reig et al., 2022).

HCC Therapy Strategies According To BCLC Stages

In the very early and early stages (0, single ≤2cm, preserved liver function & A, single or ≤3 nodules each ≤3cm, preserved liver function), patients should be considered for liver transplantation as a curative treatment option. In case a liver transplantation is not feasible, ablation should be the treatment of choice. In case of a single liver lesion with normal portal pressure and bilirubin resection should be considered. Liver transplantation should be performed for patients with intermediate stage after applying the extended liver transplant criteria (B, multinodular, preserved liver function). In case of BCLC stage B lesions which are well defined and portal flow is preserved TACE should be performed, either as terminal treatment or for downstaging, and then transplant re-evaluation. Systematic therapy should be considered if the disease is already diffuse and infiltrative. For patients in advanced stages (C, portal invasion and/or extrahepatic spread, preserved liver function), systemic treatment (Atezolizumab-Bevacizumab or Durvalumab-Tremelimumab) is advised. In case of terminal-stage disease (D, any tumor burden with end-stage liver function), BSC is recommended. Median survival based on the BCLC stages A, B, C, and D have been reported to be 59 months, 24 months, 9 months, and 5 or 11 months (excluding or including patients in stage D treated with liver transplant) (D'Avola et al., 2011).

HCC recurrence has been reported to affect up to 88% of patients (Shah et al., 2007, Tsilimigras et al., 2020). A recent study suggests that imaging data should be included when predicting HCC recurrence since it may help to improve patient selection for treatment (Iseke et al., 2023).

Preoperative Planning

Future Liver Remnant

For most patients with liver lesions, liver transplant for HCC and hepatectomy for liver metastases, are their best option for curative treatment. Nevertheless, only a limited number of patients can undergo resection due to an insufficient anticipated future liver remnant, leaving 70% of HCC patients and up to 80% of patients with liver metastases unresectable at the point of diagnosis (Van Cutsem et al., 2016, Rocha and Helton, 2012).

Methods Of Assessing Functional Liver Volume

For a long time, it was unclear how much liver needed to remain after resection, and comparison was difficult due to no standardized measuring methods. In 2002 Vauthey et. al. proposed a formula to standardize the total liver volume estimation (TELV) (Vauthey et al., 2002). Based on his findings, the FLR volume to TELV ratio was defined as the standardized FLR (Vauthey et al., 2000). Other methods to assess functional liver volume have been published in recent years. (99m) Tc-mebrofenin hepatobiliary scintigraphy with single-photon emission computed tomography (SPECT) and indocyanine green (ICG) clearance are the most broadly used ones. (99m) Tc-mebrofenin HBS can assess segmental-based liver function, helping to estimate the risk for post-hepatectomy liver failure and, therefore, increase the precision of increasing the limits of resection (de Graaf et al., 2010). Several studies reported that the ICG 15 15-minute retention rate is the best parameter to predict post-operative mortality and liver failure. Therefore, it is the most frequently used test before hepatectomy in Western countries (Hemming et al., 1992, Nonami et al., 1999).

Factors Influencing FLR Requirements

There is an ongoing debate about how much liver should remain after resection. The required remnant depends on various factors, including liver function and the underlying liver disease. Numerous studies indicated the correlation between the remaining functional liver volume and postprocedural outcomes (Vauthey et al., 2004, Ribero et al., 2007, Vauthey et al., 2000). An analysis of patients' complications after extended right hepatectomy with otherwise normal underlying liver showed that complication rates increased when the FLR was <20% (Abdalla et al., 2002). Therefore, PVE is nowadays indicated when the FLR% is less than 20% in those patients. When it comes to patients who received chemotherapy before extensive hepatectomy, PVE is recommended when the FLR% is less than 30% (Azoulay et al., 2000, Adam et al., 2004). In patients with an underlying fibrotic/cirrhotic liver an FLR% of <40% indicates that PVE is recommended before extensive hepatectomy (Shirabe et al., 1999, Kubota et al., 1997, Farges et al., 2003).

Strategies For Functional Liver Volume Increase

Several methods for FLR increase have been proposed in the last decades (Memeo et al., 2021). These include portal vein ligation (PVL), PVE, liver venous deprivation (LVD), ALPPS, or radiation hepatectomy. PVL is a method that openly or laparoscopically ligates the right or left portal branch. In comparison, in PVE the left or right portal vein will be embolized percutaneously and catheter-based (Kinoshita et al., 1986). In both methods, the main goal is to achieve stasis in the targeted vascular structure leading to inflammation and hypoxemia and promoting liver hypertrophy through genetic upregulation. No significant differences have been reported when comparing both methods concerning hypertrophy and safety. However, it is clear that because of its lower invasiveness PVE should be the preferred option (Capussotti et al., 2008, Isfordink et al., 2017). Besides, in recent years LVD was invented to increase the hypertrophy rate after PVE alone. LVD combines the occlusion of the hepatic and portal vein. These can be done simultaneously or as a two-stage procedure (Hwang et al., 2009, Guiu et al., 2016, Panaro et al., 2019). To date, its advantages over PVE alone are evaluated in the HYPERLIV-01 multicenter randomized trial (Deshayes et al., 2020). ALPPS is a method that combines PVL with parenchymal transection. At the first stage, liver lesions in the remaining liver lobe will be resected combined with PVL. At the second stage the other diseased lobe will be resected (Schnitzbauer et al., 2012). This decreases the time to complete tumor removal from 4-6 weeks to 1-2 weeks. Based on several publications, concerns have been raised due to high postoperative mortality following ALLPS. Severe complications have been reported in up to 27% of patients (Schadde et al., 2014). Since then, several modifications have been made to reduce the invasiveness, establishing ALPPS as a secondary treatment option. One of the latest inventions has been the use of radiation hepatectomy. After occluding all extrahepatic vessels, Y90 will be distributed throughout the targeted lobe (Jakobs et al., 2008). Several studies confirmed the feasibility of contralateral hypertrophy using radiation lobectomy, but its liver hypertrophy and kinetic growth rate (KGR) remain lower than in PVE (Fernández-Ros et al., 2014, Garlipp et al., 2014).

Portal Vein Embolization

Evolution Of PVE

Portal vein embolization was first introduced as a preoperative concept for HCC to improve the outcome of transcatheter arterial embolization by Kinoshita et al. (1986). Besides, it was used for preoperative treatment of patients with hilar cholangiocarcinoma to increase their FLR and test if the contralateral lobe tolerates the higher portal venous pressure induced by its contralateral portal vein embolization (Makuuchi et al., 1990). In the upcoming years, indications for PVE have been subsequently expanded to patients with other liver malignancies like colorectal cancer liver metastases. In contrast, for patients with advanced liver cirrhosis, the indication is still decided case by case.

Advantages Of Portal Vein Embolization

Compared to arterial embolization, whereas postembolization syndrome with symptoms of fever, nausea, or significant pain is frequently observed, only a minority of patients with portal vein embolization have these symptoms. Therefore, PVE is a well-tolerated and safe procedure and often performed on an outpatient basis. Besides, Abulkhir et al. (2008) reported in their meta-analysis that no procedure-related deaths were observed for PVE.

Patient Selection Criteria And Contraindications For Preoperative PVE

Selecting patients who will benefit from preoperative PVE is crucial for its success. There have been only a few guidelines indicating PVE for specific clinical situations, whereas the rest are interdisciplinary and decided on a case-by-case basis. In general, PVE should be evaluated in patients planned for hepatectomy with an insufficient FLR. Besides, the extent of hepatic resection, comorbidity, and patient performance status are vital for its selection. Avritscher et al. (2008) reported that there are only a few absolute contraindications for performing PVE. Portal hypertension and its consecutive clinical consequences are contraindications for hepatic resection and, therefore, for preoperative PVE. Besides, already redirected blood flow through portal venous thrombus or tumor invasiveness represents additional contraindications since it limits the ability to increase the FLR sufficiently.

Techniques & Approaches For Performing Portal Vein Embolization

In recent years, there have been three major approaches to performing portal vein embolization: transileocolic or transhepatic, either ipsilateral or contralateral (Shimura et al., 2007, Nagino et al., 1996, Giraudo et al., 2008). Whereas transileocolic approaches are only performed in some Asian centers because of their invasiveness and need for general anesthesia, ipsilateral or contralateral approaches are widely used with operators' choice of approach. PVE is mainly required before right or right extended hepatectomy, whereas the remaining liver is often sufficient even when left extended hepatectomy is performed. In the ipsilateral approach, access will be through the tumor-bearing liver, in contrast to the contralateral approach, where the remaining liver will be accessed. In both approaches, ultrasound

guidance will be used to puncture a distal portal branch, and a catheter will be advanced wire-guided. Portography will be performed to analyze the liver's vascular structure and portal venous pressure will be measured. In both approaches, anterior branches will be targeted because of their lower complication rates (Abulkhir et al., 2008). When segment four embolization is required, it should preferably be performed first because of the advantage in the case of non-target embolization that the right lobe is still unembolized and other treatment options can be evaluated. After successful embolization, final portography will be performed to confirm stasis in the embolized lobes and the access tract will be embolized to reduce the risk of bleeding. The ipsilateral approach should be preferred whenever possible to protect the FLR. The contralateral approach should be evaluated to reduce the risk of peritoneal seeding in case of a substantial tumor burden.

Complications And Safety Considerations Of PVE

A meta-analysis by Abulkhir et al. (2008), including 1088 patients treated with percutaneous or transileocolic approaches, reported a morbidity of 2.2% and 0% mortality. Several other studies have been published reporting adverse events in 12.8-14.5% of treated patients (Kodama et al., 2002, Di Stefano et al., 2005). Adverse events range from minor complications like fever, nausea, or coil displacement to major complications like cholangitis, subscapular hematoma, or liver abscess (Abulkhir et al., 2008). Minor complication rates of up to 25% and major complications of up to 5% are acceptable according to the PVE quality improvement guidelines (Denys et al., 2010).

Influencing Factors Of FLR Increase

Liver hypertrophy after PVE differs based on the background. The FLR increase has been reported to be 35 ± 28% after 4 to 8 weeks or 9cm^3/d at week two for those with chronic liver disease. In comparison, the FLR increased 44 ± 19% or 12 to 21cm^3/d in normal underlying liver (Madoff et al., 2002, Farges et al., 2003).

Embolic Agents

Over the past decades there have been several embolic agents that have been used for portal vein embolization including the mixture of n-butyl cyanoacrylate (NBCA) and ethiodized oil, ethanol, absorbable gelatin sponge (Gelfoam), foam-sclerosing agents, polyvinyl alcohol particles (PVA) or microspheres (Covey et al., 2008, Kim et al., 2009, Igami et al., 2014, Fischman et al., 2014).

When using NBCA or microspheres as embolic agents, their mechanism is based on causing stagnation of blood flow. Similarly, coils and plugs can create a mechanical obstruction that stops blood from flowing through the affected vessels. On the other hand, using foam-sclerosing agents or ethanol leads to portal vein necrosis.

Preferences In Embolic Agent Selection

There has been an ongoing debate on which embolic agents should be preferred in which setting. A systemic review by van Lienden et al. (2013) reported that NBCA, followed by gelatin sponge and PVA-based particles, were the three most common types of embolic agent for PVE (32.5%, 26.3%, and 14.7%). This study did not specify if microspheres were used. Besides, there are regional differences in the choice of embolic agents. Whereas Asian centers prefer absolute ethanol and European centers the use of NBCA, Microspheres, or PVA-based particles are primarily used in Northern America.

Comparative Analysis Of Embolic Agents' Efficacy

In a meta-analysis by Ali et al. (2021) different embolic agents have been compared. The FLR increased by 49.1% ± 29.7, 42.2% ± 40, 28.4% ± 4.7 or 25.7% ± 8.3, 42.1% ± 8.3 using NBCA, microspheres, ethanol, gelfoam, and sclerosing agents, respectively. Technical and growth success rates were >90% in all groups. Technical success was highest in the NBCA group (99.4%), whereas growth success was highest in the gelfoam group (98.2%). Technical failures were mostly related to incomplete embolization and, therefore, recanalization. Complication rates after PVE varied between the embolic agents. Major complications have been observed mainly in the ethanol group, with 8% and cholangitis being the most common cause. Minor and overall complication rates were lowest for microspheres, with 11% and 16%, respectively. Multiple investigations, including a recent prospective clinical trial, have shown that NBCA yields a more substantial increase in FLR volume in healthy underlying liver compared to particles and coils (Ali et al., 2021, Guiu et al., 2013, Luz et al., 2021). In contrast, the study by Kuhn et al. (2023) indicates that microspheres and coils achieved a higher degree of liver volume increase in normal underlying liver than NBCA after two weeks, achieving similar results after four weeks (58.4% vs. 46% & 60.5% vs. 60.4%). These results were consistent for cirrhotic livers as well (52.2% vs. 47.2% & 54.9% vs. 54.2%).

Study Limitations In Embolic Agent Research

Most of the studies published in this area have certain limitations that could impact the reliability of their conclusions. For instance, cirrhotic patients are typically excluded, and there is often an operator experience bias where one agent is used more frequently than the other. Given the significant consequences of inadequate liver function on patient's survival, it becomes evident that individuals in such circumstances would particularly benefit from a rapid resection. Additionally, when microparticles are used, the size of the embolic is often not mentioned. It has been shown that these factors, either alone or in combination, can have severe implications for the regenerative potential of the FLR (Luz et al., 2021, Madoff et al., 2005b, de Baere et al., 2009). As a result, it is essential to approach these studies' findings with caution and consider these limitations when interpreting the results.

Aims Of This Work

From the first publication of PVE by Kinoshita et al. (1986) to date, several papers have been published concerning different techniques, embolic agents, and methods. Still, PVE remains the standard of care worldwide for patients with insufficient FLR before resection. Nevertheless, the embolic agent of choice remains a controversial topic. Notably, in patients with underlying liver disease, very little data was published, underrepresenting this group in most studies, making evidence-based decisions challenging. Therefore, in those high-risk situations of patients with reduced liver function and hypertrophy potential, the choice of an embolic agent could have severe implications on their survival and clinical outcomes. This work was designed to answer the remaining question of the preferred choice of embolic agent in cirrhotic livers under minimized potential biases.

Original Published Paper

Kuhn TN, Kahl VH, Wang Y, Berz AM, Shewarega A, Santana JG, Antoch G, Chapiro J, Schlachter T, Madoff DC. Hepatic Hypertrophy in Normal and Cirrhotic Livers Following Portal Vein Embolization: Comparative Assessment of 2 Different Embolic Regimens in a Large Animal Model. J Vasc Interv Radiol. 2023 Dec;34(12):2162-2172.e2. doi: 10.1016/j.jvir.2023.08.024. Epub 2023 Aug 25. PMID: 37634850.

Discussion

This study supports the hypothesis that microspheres are the preferred choice of embolic agents in comparison to NBCA. This is the case for a normal underlying liver, but particularly for a diseased cirrhotic liver where quick and long-term FLR increase is essential for patients' survival. Furthermore, the results emphasize that follow-up imaging may be performed two weeks post-PVE already when microspheres and coils are used. Moreover, the correlated hypertrophy kinetics observed with micropsheres and coils showed that the main FLR increase was within the initial first two weeks. This discovery provides a foundational basis for establishing decision criteria aimed at expanding the inclusion of patients eligible for portal vein embolization (PVE), especially those in critical need of resection.

Advantages Of Large Animal Models In Evaluating Embolic Agent Selection

Most recent studies about the choice of embolic agents were clinical trials. Whereas those studies have the advantages of studying humans under real-world conditions, they often lack clear data, including precise follow-up imaging dates, identical underlying liver conditions, and similar pretreatment, which biases their results. Therefore, this study preferred a large animal model offering similar vascular and liver anatomy as well as similar response by the immune system to induced regeneration. As such hypertrophy kinetics may be evaluated best in such an idealized experimental setting (Ntonas et al., 2020, Nykonenko et al., 2017).

There are several animal models of fibrosis or cirrhosis; chemical induction by carbon tetrachloride (CCL4) is the most commonly used one, especially in mice models (Scholten et al., 2015). Other options include Thioacetamide-induced, alcohol-induced, or transgenetic models (Bao et al., 2021). All small animal models have in common that they mimic a cirrhotic liver but are unsuitable for using catheters and embolic agents. In this study, no animal had significant long-term lab value changes, likely due to the rapid induction method. Even so, histologically confirmed cirrhosis could be confirmed in all animals, proving the effectiveness of both the acute damage caused by ethanol administration and the persistent damage induced by ethiodized oil (Avritscher et al., 2011).

Immunological And Histological Insights

Liver cirrhosis is a complex disease that develops over time. During this period, several immune cells contribute to the liver's inflammation and fibrotic tissue remodeling. A recent study by Zimmermann et al. (2010) identified a subset of CD14(+)CD16(+) positive monocytes that were proven to be part of the intrahepatic inflammation and profibrogenic hematopoietic stem cell (HSC) activation that drives fibrogenesis in the liver. Similar results were published in a study by Liaskou et al. (2013) , which showed increased levels of T-cell proliferation and proinflammatory and profibrogenic cytokines levels associated with CD16(+) positive monocytes. These CD16(+) levels were associated with the acuteness of liver damage (Singanayagam and Triantafyllou, 2021). CD3 as a T-cell marker and CD16 for

macrophages were both shown to be significantly elevated in the cirrhotic groups in this study, underlining the permanent liver damage of the model and replicating the findings of the studies mentioned before.

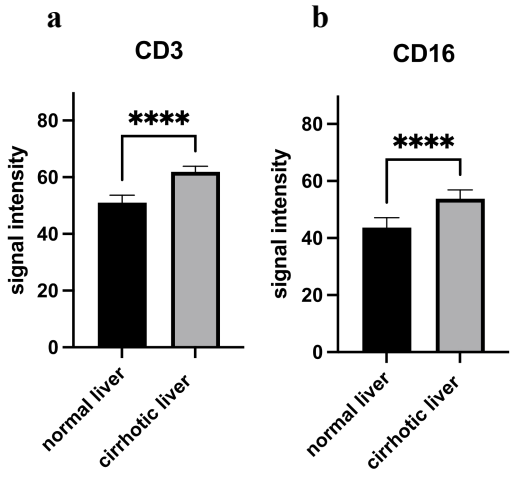

Fig. 2a CD3 expression comparing normal versus cirrhotic underlying liver. **b** CD16 expression comparing normal versus cirrhotic underlying liver. This figure was published in the Journal of Vascular and Interventional Radiology (JVIR), Vol number 34, Kuhn, T.N. et al., Hepatic Hypertrophy in Normal and Cirrhotic Livers Following Portal Vein Embolization: Comparative Assessment of 2 Different Embolic Regimens in a Large Animal Model., Page No 2167, Copyright Elsevier (2023), **** $p<0.0001$.

A study published by Bantel et al. (2001) showed a correlation between inflammatory liver injury and the expression levels of Caspase 3 in chronic underlying liver, concluding that Caspase 3 could be a valuable marker for liver damage. Additional studies found that Caspase 3 inactivation reduces apoptosis levels in methionine- and choline-deficient-fed fibrotic mice models (Thapaliya et al., 2014). This matches the findings in this study in which Caspase 3 was elevated particularly in the cirrhotic liver groups, which may be associated with the liver damage induced by the administration of ethanol and ethiodized oil.

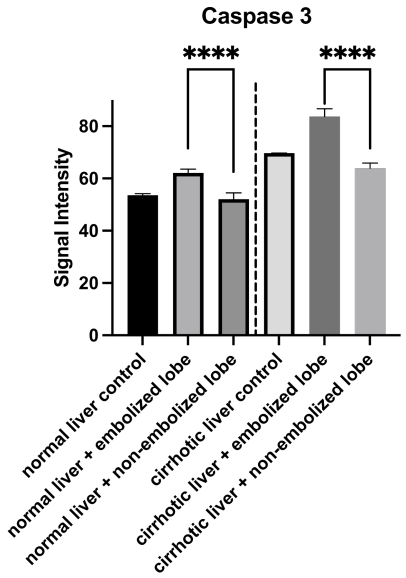

Fig. 3 Caspase 3 levels comparing the embolized versus non-embolized lobe in normal versus cirrhotic underlying liver. This figure was published in the Journal of Vascular and Interventional Radiology (JVIR), Vol number 34, Kuhn, T.N. et al., Hepatic Hypertrophy in Normal and Cirrhotic Livers Following Portal Vein Embolization: Comparative Assessment of 2 Different Embolic Regimens in a Large Animal Model., Page No 2167, Copyright Elsevier (2023), **** p<0.0001.

Ki67 was used as a proliferation marker, which was shown to have reduced expression in the cirrhotic group compared to the normal underlying liver. Furthermore, Ki67 expression was elevated in the non-embolized lobes and reduced in the embolized lobe. This was the case for normal and cirrhotic groups. Follow-up imaging was able to confirm these molecular findings. Therefore, Ki67 expression could be a valuable prediction marker for successful PVEs. Despite the reduced regenerative potential in the cirrhotic group, it was adequate to undergo following hepatectomy, therefore underlining the potential for preoperative PVE in cirrhotic patients (Sun et al., 2018, Guglielmi et al., 2012).

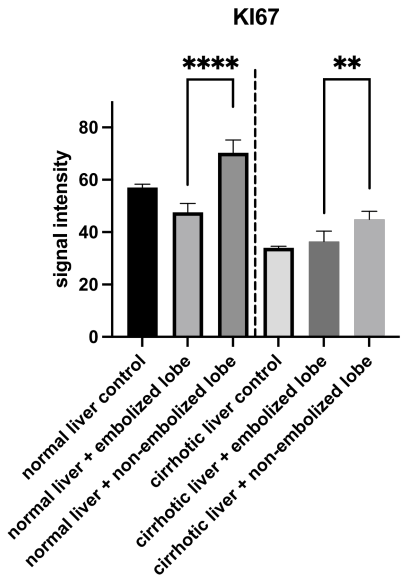

Fig. 4 Ki67 levels comparing the embolized versus non-embolized lobe in normal versus cirrhotic underlying liver. This figure was published in the Journal of Vascular and Interventional Radiology (JVIR), Vol number 34, Kuhn, T.N. et al., Hepatic Hypertrophy in Normal and Cirrhotic Livers Following Portal Vein Embolization: Comparative Assessment of 2 Different Embolic Regimens in a Large Animal Model., Page No 2167, Copyright Elsevier (2023), **** p<0.01,**** p<0.0001.

Alternative Techniques & Therapies

ALPPS was first introduced by Schnitzbauer et al. (2012), who included 25 patients with primary liver cancer (n=9) or metastatic disease (n=16). They reported a FLR increase of about 74% after a median of 9 days. These findings were repeatedly confirmed, ranging from 68-80% within a week (Schadde et al., 2014, Eshmuminov et al., 2016, Sandstrom et al., 2018). Moris et al. (2018) compared the outcome of ALLPS vs. two-stage hepatectomy in their meta-analysis of 657 unresectable CRC metastases. Whereas they reported a more rapid FLR increase (19.07ml/d), the final postoperative FLR was not significantly

different. Besides, they reported a lower overall and major morbidity when PVE was used. Whereas the initial results were promising, the method is limited by its high morbidity or mortality. Schadde et al. (2014) reported a 90-day mortality rate of as high as 9%, which was already reduced to previously published studies (12%, (Schnitzbauer et al., 2012)). Besides, 44% of patients experienced grade 3 or 4 events that required interventions or reoperation (grade 3) or were life-threatening (grade 4) (Schnitzbauer et al., 2012). At first, these findings were believed to be associated with the invasiveness of the method, but further analysis of the International ALPPS Registry reported that the leading cause for the 90-day mortality was liver failure 75%, (Schadde et al., 2015). This drove the hypothesis that the high mortality and morbidity were rather due to an insufficient liver parenchyma than the invasiveness of the procedure. Further sub-analysis histologically confirmed that the canalicular-ductule network was poorer in patients treated with ALPPS, which could be associated with prolonged cholestasis after resection (Matsuo et al., 2017). Matsuo et al. (2016) reported similar results, which have shown the immaturity of hepatocytes in the FLR after ALPPS vs. PVE. These lead to several modifications of the method, including a combination with radiofrequency, "non-touch" techniques, or minimal first-stage ALPPS, but have been only performed in a minority of patients (de Santibanes et al., 2016, Li et al., 2016, Gall et al., 2015).

Therefore, ALPPS remains a secondary treatment option for those patients where either PVE fails to achieve sufficient FLR increase or the benefit outweighs the risk (Tanaka et al., 2015).

Evolution Of Portal Vein Embolization

Portal vein embolization was first introduced by Kinoshita et al. (1986), who included 21 patients with hepatocellular carcinoma. Since then, embolic agents, catheters, and methods have advanced. In the most recent meta-analysis by Wajswol et al. (2018) including 607 patients the mean FLR increase was reported to be 49.4% ±1.3%. These results are comparable with this study in which animals treated with PVE + MC achieved a mean FLR of 60.5% ±3.9% and 60.4% ±3.5% when treated with NBCA after four weeks. Several other meta-analyses reported a similar FLR hypertrophy ranging from 37.9-43.2% (van Lienden et al., 2013, Isfordink et al., 2017). Morbidity and PVE-related mortality were reported to be between 2.2-3.9% and >0.1%, making it the safer option than ALPPS (van Lienden et al., 2013, Isfordink et al., 2017, Wajswol et al., 2018, Abulkhir et al., 2008). There was no mortality been reported for this study. The rate of successful resection ranges from 75.9% to 85%, therefore lower than for ALPPS (Abulkhir et al., 2008, van Lienden et al., 2013, Wajswol et al., 2018). In recent years, both ipsilateral and contralateral approaches have been used. To date, technical success rates >95% have been reported despite the approach or embolic agents used (Kinoshita et al., 1986, Makuuchi et al., 1990, Ribero et al., 2007, Madoff et al., 2005a, Di Stefano et al., 2005, Fischman et al., 2014, Bent et al., 2009, Guiu et al., 2013, Abulkhir et al., 2008, Wajswol et al., 2018). Therefore, the approach is based on the operators' choice and experience. Whereas PVE was often discussed to be insufficient, especially in cirrhotic livers, this study indicated otherwise and paved the way for standardized preoperative PVE in cirrhotic livers. Despite the sFLR% increase being lower than that of the normal underlying liver, an

increase of +10.93% was still achieved, deemed adequate for subsequent resection. These findings exhibited consistency irrespective of whether PVE was conducted with MC or NBCA.

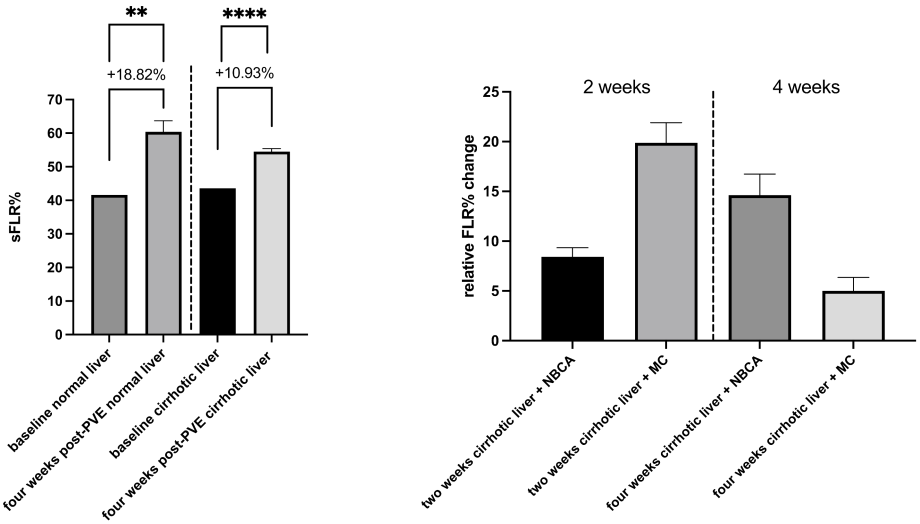

Fig. 5a Absolute sFLR% increase in normal and cirrhotic underlying liver after four weeks. **b** Relative FLR% change comparing PVE with MC versus NBCA in cirrhotic underlying liver after two and four weeks. This figure was published in the Journal of Vascular and Interventional Radiology (JVIR), Vol number 34, Kuhn, T.N. et al., Hepatic Hypertrophy in Normal and Cirrhotic Livers Following Portal Vein Embolization: Comparative Assessment of 2 Different Embolic Regimens in a Large Animal Model., Page No 2169, Copyright Elsevier (2023), ** $p<0.01$. **** $p<0.0001$.

Some argue that PVE leads to tumor progression either because of the time between PVE and hepatectomy or because of the release of growth factors induced by PVE. Therefore, some strategies have been developed in recent years that are now out for clinical evaluation (Tanaka et al., 2015).

New Strategies And Future Directions

Transarterial Embolization & Portal Vein Embolization

One of them is the subsequent or combined trans-arterial embolization (TAE), which additionally occludes the arterial tumor supply, which may reduce the risk for disease progression between PVE and resection (Imamura et al., 2008, Nakao et al., 1986, Simoneau et al., 2012, de Graaf et al., 2009, Ogata et al., 2006, Aoki et al., 2004, Yamakado et al., 1999, Yamakado et al., 1994). Besides, it reduces the risk for post-PVE hepatic arterial buffer response, associated with increased arterial blood flow into the embolized lobe, hypothesized to reduce the effectiveness of PVE (Imamura et al., 2008, Nakao et al., 1986). Still, the main limitation remains the risk of necrosis of the non-tumor-bearing parenchyma after additional arterial embolization. Therefore, the technique was widely modified with days to weeks in between (Yamakado et al., 1997, Aoki et al., 2004, Ogata et al., 2006). In most cases, TAE is performed first followed by PVE. In a case report by Gruttadauria et al. (2006), PVE was initially performed, followed by TAE. This was hypothesized to increase the outcome by leaving the more invasive treatment of TAE only for those with insufficient initial FLR. Nevertheless, in most studies, the combined

approach has been used because of its higher expected FLR increase in comparison to PVE alone (12% vs. 8% & 7.3% vs. 5.8% (Ogata et al., 2006, Vilgrain et al., 2008). Interestingly, the only multicenter study concerning this topic reported no significant difference in FLR increase in PVE+TAE vs. PVE (7.4% vs. 7.9%, p=0.203). However, a significantly higher amount of patients with the status "alive without evidence of disease" was reported($p<0.01$), supporting the hypothesis of reduced disease progression after TAE (Peng et al., 2012).

Whereas elevated transaminase levels have been reported several times, the initial concern of necrosis of non-tumor-bearing parenchyma could not be confirmed in histological evaluations (Yamakado et al., 1997, Imamura et al., 2008, Aoki et al., 2004). In contrast in this study PVE lead to no elevation of transaminase and no necrosis was observed histologically. Some authors even suggest that PVE+TAE could be an adequate therapy option for patients who do not achieve the inclusion criteria for following resection (Yamakado et al., 1999, Ogata et al., 2006, Vilgrain et al., 2008). This can even be safely performed when PVE was insufficient initially (Kang et al., 2009, Wallace et al., 2008).

Hepatic Vein & Portal Vein Embolization

A recent additional adaptive method has been LVD, which includes a subsequent or combined embolization of the hepatic vein, mainly the right hepatic vein, with PVE (Hwang et al., 2009, Ko et al., 2010). This method mostly has two advantages: the reduced arterial buffer response by eliminating the outflow of the liver and the reduced potential of necrosis otherwise associated with TAE. In recent years, the technique has been modified. Guiu et al. (2016) have shown that combined PVE and hepatic vein embolization (HVE) is safe and feasible and that the transhepatic approaches can be performed without additional risk. Although only small studies exist, Kobayashi et al. (2020) reported a higher FLR increase after 22 days vs. 26 days when comparing LVD with PVE (135% vs. 124%, p=0.034). This study reported an increase of 118.82% after four weeks being compatible with the results published. Besides, the kinetic growth rate was also significantly higher (2.9%/week vs. 1.4%). Nevertheless, in a recent study published by Cassese et al. (2023) comparing the short and medium-term outcomes of 17 (LVD) vs. 16 (PVE) patients, the median disease-free survival was 6 vs. 12 months (p=0.29). Besides, the 3-year survival was 54.7% vs. 77.4% but did not reach statistical significance (p=0.64). The KGR and the FLR increase were comparable to previously published studies ($10cm^3$/day vs. $4.8cm^3$/day; 49% vs. 27%).

Since only small single-center studies have been performed, evidence-based decisions are difficult to make. Therefore, two multicenter randomized trials ((HYPERLIV-01, NCT03841305; DRAGON 2, NCT05428735)) comparing LVD vs. PVE are currently being conducted. In both studies PVE is performed either alone or in combination; therefore, the quality of PVE plays a crucial role in the outcomes of these trials. Hence, the distinct growth kinetics observed with MC and NBCA in this study warrant further subanalysis within these clinical trials. Additionally, there is an ongoing follow-up project comparing LVD with PVE in a cirrhotic background that will be published soon.

Extended Liver Venous Depriviation

Some authors suggest extended LVD (eLVD), which includes the embolization of the middle hepatic vein as an alternative to ALPPS. Le Roy et al. (2017) showed that the KGR is dependent on the amount of embolization, which increases from 4.4cm^3/day to 9.3cm^3/day to 25cm^3/day when PVE, LVD, and eLVD were performed. ALPPS is often limited by the increased morbidity and mortality even after rapid FLR increase due to insufficient liver function. A recent study by Sparrelid et al. (2017) comparing the liver function post eLVD or ALPPS using 99mTc-mebrofenin hepatobiliary scintigraphy provided evidence that the FLR increase after eLVD results in more functional liver volume, reducing the risk for post-hepatectomy failure (65.7% vs. 28.2%). Still, large multicenter randomized trials are needed to provide evidence for decision-making.

Radioembolization

Another therapy alternative is the use of radioembolization, which was found to be effective as well. In recent years, yttrium-90 was used as a treatment option for HCC or other secondary malignancies. During these procedures, it was recognized that the ipsilateral lobe reduced in size, whereas the contralateral lobe increased in size (Siddiqi and Devlin, 2009, Gulec et al., 2009, Jakobs et al., 2008, Gaba et al., 2009). This led to the hypothesis that radioembolization could be used as a treatment option for FLR increase. In comparison to Y-90 treatment for tumors alone, higher dosages and more proximal administration are needed, leading to radiation of the non-tumor-bearing liver (Malhotra et al., 2019). This method can either be used as a definitive or bridging treatment. In addition, Vouche et al. (2013) reported that the presence of portal vein thrombosis leads to a higher degree of FLR increase, which is a contraindication for patients treated with PVE. Due to the relatively recent use of this method, no standardized method has been implemented, making comparison of studies difficult. A recent systemic review including 312 patients who underwent radioembolization has shown that Y-90 treatment resulted in FLR hypertrophy between 26-46% (44 days - 9 months) (Teo et al., 2016).

Compared to PVE, the FLR increase was lower in patients treated with Y-90 (61.5% vs. 29.0%). Similar results were published concerning the KGR (Fernández-Ros et al., 2014, Vouche et al., 2013). Therefore, radioembolization could be used as a viable treatment option for patients who will not undergo hepatectomy, and therefore, a rapid FLR increase is unnecessary.

Comparative Analysis of Embolic Agents

Over the past decade, several embolic agents have been published. In their meta-analysis, van Lienden et al. (2013) reported that NBCA, gelatin sponge, and PVA-based particles have been the most common embolic agents. Even if they reported that the degree of liver hypertrophy using NBCA was higher than for microspheres and coils, the difference was not statistically significant.

In recent years, several publications have been published favoring NBCA as the preferable embolic agent (Ali et al., 2021, Guiu et al., 2013). In contrast, our study, which is based on an ideal setting with very few confounding variables, supports microspheres and coils as the embolic agent of choice. In this

study MC outperformed NBCA, allowing for earlier follow-up imaging and curative resection within two weeks. These consistent results, especially vital for the cirrhotic group, underscore the critical need for rapid resection in patients with compromised liver function and diminished survival prospects. Consequently, this study advocates for the prioritized utilization of MC in patients with impaired liver function.

Methodological Considerations

In most studies, fibrotic or cirrhotic patients have been underrepresented, with only 17.3% of the population. This representation varied from 1% for studies using sclerosing agents to 26% using Gelfoam. Only about 10% of the patients for trials using microparticles or NBCA had an underlying cirrhotic or fibrotic liver disease (van Lienden et al., 2013). Therefore, evidence-based conclusions for those cohorts are challenging.

There is consensus that embolization should be as distal as possible to reduce the risk of recanalization and collateral blood flow, which would reduce the effectiveness of PVE. In most studies, including a recent randomized trial, the particle size is not described, which could significantly affect the outcome (Luz et al., 2021). NBCA is influenced by various factors, including the ratio of ethiodized oil and NBCA, blood contact time, or the application method (Hill et al., 2018). Microparticles have the advantage of choosing the accurate particle size of each targeted vessel reducing the risk of non-target embolization. This could explain the higher minor and overall complication rates for NBCA in comparison to microspheres and coils, which have been reported in the meta-analysis by Ali et al. (2021) (19% vs. 11% & 23 v. 16

Recent studies have shown reduced procedure times, reduced fluoroscopy times, and lower material costs for NBCA in comparison to microparticles. Most centers have only substantial experience with NBCA, leading to operator bias (Ali et al., 2021). To eliminate this bias in our study, each embolic agent was used by experts in their field with extensive experience. However, Jaberi et al. (2016) reported similar surgical outcomes between the use of NBCA and polyvinyl alcohol particels, including rates of resection complications, the number of patients who failed to include the inclusion criteria for resection, duration of hospitalization and entry rates into the intensive care unit ($p=0.3$, $p=1.0$, $p=0.68$, $p=0.71$).

Study Limitations

There are several limitations when it comes to this research. In this work, an animal model was used to address the topic. The cirrhosis induction is based on an infusion of ethiodized oil and ethanol. With this approach come some disadvantages: Using ethanol and ethiodized oil mainly mimics ethanol-induced liver damage but leaves out virus- or metabolic-induced ways of cirrhosis induction like Lee et al. (2009) described in their paper.

Nevertheless, this model was variously used and led to biopsy-confirmed cirrhosis after four weeks. Besides, this model lacks the existence of tumors in the liver. Schachtschneider et al. (2017) published a paper stating that by implementing specific mutations, HCC could be created in the liver. Treatment of a tumor was, however, not the focus of this study. Additionally, only HCC can be created, leaving out the largest group of patients with secondary liver cancer. Compared to humans, where cirrhosis develops over years and years of repeated damage, this model induces cirrhosis in four weeks, which could lack hypertrophy influencing factors and, therefore, influence the outcome. However, this model is well established and can be performed in a reasonable time frame.

A second limitation of this work is follow-up imaging. Even if two follow-up imaging time points have been performed, this only led to data from two-time points and leaves room for interpretation for the time frame in between. In this study it was hypothesized that the liver would grow linearly. Even if most studies perform similar ways of analyses, it must be mentioned that a work by Li and Madoff (2016) showed that the liver grows exponentially after stimulation and reaches a plateau after 30 days. An increased number of imaging time points and an extended follow-up period could have led to different conclusions and would have limited potential bias arising from unsupervised time in between. Nevertheless, the highest degree of hypertrophy should have been captured with an additional time point after two weeks.

When ALPPS was first introduced, it showed promising results with a higher degree of FLR increase. However, a detailed analysis of the liver function presented poorly developed Hepatocytes with reduced function (Matsuo et al., 2016). Therefore, additional (99m)Tc-mebrofenin hepatobiliary scintigraphy would have been beneficial rather than liver volume changes themselves (Sparrelid et al., 2017). Besides, performing hepatectomy would have delivered essential information about the anticipated outcomes of the two compared embolic agents. Nevertheless, patients receiving PVE mostly only undergo one follow-up CT imaging to decide if they fulfill the inclusion criteria for following resection, and these studies focused on PVE rather than surgical outcomes.

When it comes to the statistical power of this study, the size of only three animals reduces its validity. However, this study was performed in large animals, and therefore, the number was limited by federal regulations and financial support. Still, comparable studies that were performed consisted of similar group sizes (de Baere et al., 2009, Avritscher et al., 2011, Madoff et al., 2007).

Compared to humans, where organ size changes minimally in adolescents, large animals like pigs have underlying liver hypertrophy that occurs naturally. Therefore, the liver increases in size without any stimulation and is based on the amount of food provided. To take this fact into account, control animals

for both groups, normal and cirrhotic underlying liver, that were fed and held under similar conditions, were used to follow-up on the naturally occurring liver growth. All animals included in this study were then standardized based on their controls, reducing the natural bias.

Several additional methods have been developed in recent years to increase the safety and effectiveness of induced FLR increase, including radioembolization, LVD, or PVE+HAE. This study solely focused on PVE, comparing no other methods. However, the results of this study can help choose the correct embolic agents for PVE-based methods, like LVD or PVE+HAE, since the effects should be similar. Nevertheless, our lab will publish another study soon comparing different embolic agents for LVD using the identical animal model.

Conclusion and Clinical Implications

To conclude, this work provides evidence for the controversial topic of choosing the embolic agent in PVE. Based on the data of this study, patients in high-risk situations, with critical liver function, who need curative resection in a timely manner, microparticles and coils should be chosen rather than NBCA. These findings were consistent for both normal and cirrhotic underlying livers. In addition, a shorter follow-up imaging time point of two weeks post-PVE should be considered for patients treated with microparticles and coils.

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