Radiological aspects of portal vein embolization
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Citation for published version (APA):
van Lienden, K. P. (2012). Radiological aspects of portal vein embolization

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Chapter

General introduction and outline of this thesis
General introduction

For patients with a primary liver malignancy or with metastatic liver disease, surgical resection is the only curative option. Additional techniques such as radio frequency ablation allow even more patients to undergo resection especially in bilobar disease. Extended liver resections however bear the risk of postoperative liver failure, particularly when the future remnant liver (FRL) is small or when patients have a compromised liver due to cirrhosis, cholestasis, steatosis or chemotherapy. Postoperative liver failure remains difficult to treat and results in a mortality rate of approximately 80% of patients.

Therefore, preoperative risk assessment in patients considered for extensive liver resection is of utmost importance. The minimal required volume of the future remnant liver (FRL) is considered to be 25-30% in patients with otherwise normal liver parenchyma and 40% in patients with a compromised liver. To date, the most common method of preoperative evaluation of the remaining liver volume is CT-volumetry.

Although CT volumetry enables accurate measurement of FRL-volume, it provides no information regarding the quality of the liver parenchyma in terms of functional capacity and therefore, does not reflect liver function. Quantitative liver function tests are therefore necessary, to have a better understanding of the functional FRL-volume in the work-up for liver resection. The indocyanine green (ICG) clearance test is the most widely used dynamic liver function test. A tricarbocyanic green dye is used which, after intravenous injection, is exclusively removed by the liver and excreted into the bile. More recently an alternative liver function test has been developed in our Institution using Technetium-99m-labelled Iminodiaceticacid (IDA) analogues which are excreted in the same way as ICG, using the same biliary transporters. 99mTc-mebrofenin hepatobiliary scintigraphy (HBS) correlates well with the ICG clearance test and provides additional 3-D information on segmental liver function, which proves useful in planning the liver resection.

When the anatomical or functional FRL volume is too small, there are several techniques to induce hypertrophy, increasing the volume of the FRL, after which liver resection is enabled. The mythological story of Prometheus demonstrates that the ancient Greeks already had knowledge about the regenerative capacity of the liver.

In 1920 Rous and Larimore observed in rats, that ligation of portal branches caused atrophy of the ligated liver and compensatory hypertrophy of the non-ligated remaining liver, hence demonstrating the induced regenerative capacity of the liver. In 1965, portal vein ligation (PVL) was reported in humans as part of a two-stage extended hepatectomy. Kinoshita et al. reported the first preoperative portal vein embolization (PVE) in a human being in 1986. Since then, numerous reports have shown the efficacy of inducing compensatory hypertrophy of the FRL after PVE or PVL in preparation of surgical resection.

Several techniques of portal vein occlusion have been reported, including intraoperative portal branch ligation and trans-ileocolic PVE, and the percutaneous transhepatic ipsilateral or contralateral PVE techniques. Occlusion of the portal...
venous blood flow to the liver segments to be resected, induces atrophy of the ipsilateral and compensatory hypertrophy of the contralateral, non-embolized liver segments, resulting in increase of FRL-volume. This regeneration response is generated via a complex interaction of cytokines, growth factors and metabolic networks.

The question arises however, what is the most effective augmentation technique when it comes to the extent of the induced hypertrophy response. In addition to the different techniques, different embolization materials are used clinically, e.g. polyvinyl alcohol particles (PVA), coils, gelatin sponge, n-butyl cyanoacrylate and lipiodol, fibrin glue or combinations of these agents. The efficacy of the different embolization materials on the hypertrophy response in percutaneous portal embolization is also discussed in literature.

Since patients are increasingly included in neoadjuvant chemotherapy regimens, the influence of chemotherapy on the hypertrophy response of the FRL is also under debate. Some authors report that chemotherapy does not affect the hypertrophy response at all (27), whereas others conclude that chemotherapy has a negative influence on the rate of hypertrophy.(28,29) The role of cholestasis in regeneration of the FRL after PVE also remains controversial. It is stated by some authors that longstanding cholestasis, as is usually encountered in patients with hilar cholangiocarcinoma, impedes the hypertrophy response of the FRL, emphasizing the need for pre-procedural biliary drainage.(30) This notion however, has not been confirmed in other studies.(31) Finally, patients with pre-existing liver cirrhosis have an impaired hypertrophy response and a higher risk of post-resectional liver failure.(32) The role of cholestasis in regeneration of the FRL after PVE also remains controversial. It is stated by some authors that longstanding cholestasis, as is usually encountered in patients with hilar cholangiocarcinoma, impedes the hypertrophy response of the FRL, emphasizing the need for pre-procedural biliary drainage.(30) This notion however, has not been confirmed in other studies.(31) Finally, patients with pre-existing liver cirrhosis have an impaired hypertrophy response and a higher risk of post-resectional liver failure.(32)

The technical success rate of PVE in literature approaches nearly 100%. The clinical success rate however is approximately 85%. Reasons of unresectability are local tumor progression, distant metastases, newly developed metastases in the FRL or insufficient hypertrophy response, despite technically successful PVE.(35) To decrease the percentage of patients who have an insufficient hypertrophy response, new techniques are being developed. New embolization materials are used, causing more periportal tissue reaction, and hence inducing a stronger hypertrophy response. Also sequential embolization techniques are developed in which embolization of the portal vein is followed by embolization of the hepatic vein or hepatic artery with an interval of several weeks. (36,37)

Although PVE nowadays is an accepted method to increase the resectability rate of patients with liver tumors, there is a major drawback which is a major concern. Several studies describe enhanced tumor growth after PVE (38,39) as a result of cytokines, growth factors and an increased arterial blood supply, although the exact mechanisms of this phenomenon are still largely unknown. Growth of tumor may be accelerated, while micrometastases in the non-embolized remnant liver may also develop or progress. The potential boost of tumor proliferation, therefore, creates a dilemma in terms of optimal waiting time until resection. A possible solution might be found in super selective embolization of the hepatic artery prior to PVE, as it probably prevents compensatory hyperperfusion of the tumor through the hepatic artery, thereby curbing tumor growth. It has also been
shown that sequential hepatic artery embolization and ipsilateral portal vein embolization supports the hypertrophy response of PVE. (40)

Although the technique of liver augmentation using portal vein embolization already exists for decades, there are still many questions that need to be elucidated.

**Aim of this thesis**

In this thesis, the value of functional scintigraphic liver imaging in addition to regular CT-volumetry, is assessed, especially for risk assessment in preparation of extended liver resection.

Based on experimental and clinical studies, answers will be given to questions such as, which augmentation technique is superior in inducing liver regeneration, which factors influence the hypertrophy response and which modifications to standard PVE can be devised, to increase the hypertrophy response of the non-embolized liver lobe, at the same time preventing increase of tumor growth.

**Outline of this thesis**

Since the first report on clinical application of portal vein embolization, many articles on this subject have been published. **Chapter 2** provides a systematic review of the literature on portal vein embolization over the last 20 years (1990 and 2011). The technical and clinical success rates are discussed, as well as the influence of the used embolization materials on the hypertrophy response. Special interest is devoted to the effect of liver cirrhosis, steatosis, cholestasis and pre-operative chemotherapy on the hypertrophy response of the future remnant liver.

In **chapter 3**, the outcomes are presented of patients who underwent portal vein embolization in our institution, prior to (a planned) liver resection. Especially the effect of pre-damaged liver parenchyma (cirrhosis, steatosis, cholestasis and chemotherapy) on the hypertrophy response is assessed in this chapter.

After initial reports of portal vein ligation to induce hypertrophy of the non-ligated liver segments, intra-operative and percutaneous embolization methods have been developed. In literature there is still discussion on which technique is more effective in inducing hypertrophy of the FRL. In **chapter 4**, we therefore evaluated the difference in hypertrophy response after PVL and PVE in a standardized rabbit model of PVE(41). In patients who underwent PVL, as part of a two-stage liver resection, a revascularized portal system was seen on CT-scan three weeks after PVL. To examine portal revascularisation after PVL, intra-operative portograms were made in patients who had undergone portal occlusion, at the time of laparotomy. The results are presented in **chapter 5**, in which twenty-one patients are described who underwent PVL or PVE. In all patients who had undergone PVL, collateral flow was seen through an intrahepatic, left-to-right portal venous collateral system. This process of portal
revascularization explains the inferiority of PVL in the hypertrophy response in patients and confirms the results in the rabbit model of chapter 4.

The use of absorbable embolization materials for PVE could be advantageous, especially in patients who finally appear unresectable. For optimizing the technique of portal vein embolization, the use of different embolization materials is described in chapter 6. The use of absorbable versus permanent embolization materials, and the respective effect on the hypertrophy response was evaluated in a standardized rabbit model of PVE.

In patients who clinically fail PVE because of insufficient hypertrophy response, sequential embolization of portal vein and hepatic artery or portal vein and hepatic vein, have been described in literature. In chapter 7, our standardized rabbit model is used to evaluate the additional short-term effect on hypertrophy response of hepatic vein embolization in combination with portal vein embolization. To eliminate the influence of the time factor after PVE and to achieve the maximum hypertrophy result in a short follow-up period, we performed the PVE and HVE in one single procedure instead of sequentially.

The possibility of performing an extended liver resection is dependent on the volume of the remnant liver. As CT-volumetry gives no functional information, $^{99m}$Tc-mebrofenin hepatobiliary scintigraphy (HBS), as functional modality, is compared to the volumetric data of the standard CT-scan. The additional value of $^{99m}$Tc-mebrofenin-HBS in estimating the risk of postoperative liver failure, especially in patients with uncertain liver function, is evaluated.

In chapter 9, $^{99m}$Tc-mebrofenin-HBS is combined with single photon emission computed tomography (SPECT). This enables the measurement of functional liver volume in a 3-dimensional manner and makes adequate, functional segmental delineation possible. The additional value of $^{99m}$Tc-mebrofenin-SPECT for the measurement of segmental liver function and liver functional volume is evaluated in this chapter.

Chapter 10 discusses the use of $^{99m}$Tc-mebrofenin-HBS with SPECT in a group of patients who underwent portal vein embolization prior to extensive liver resection. A comparison of the future remnant liver-volume (FRL-V) and functional future remnant liver (FRL-F) before and after PVE is made. The additional value of FRL-F over FRL-V in determining the optimal waiting time between PVE and surgical resection is evaluated, against the background of performing a safe resection.

There is increasing evidence that PVE not only stimulates growth of the FRL, but also increases tumor size because of growth factors and cytokines released in the process of liver regeneration. The challenge for future use of PVE is to limit the growth of tumor while inducing a maximum hypertrophy response in the non-embolized liver lobe. Therefore, in chapter 11, we devised an animal model in rabbits, in which the rate of tumor growth could be assessed in relation with PVE, closely resembling the clinical situation. In this rabbit tumor-model, PVE is performed using the same methods and imaging protocol used in patients undergoing PVE. The combination of a VX2 liver tumor in this rabbit model allows us, in addition, to explore the effects of PVE on tumor kinetics and at the same time, to assess the hypertrophy response of the non-embolized liver lobe.
After we studied this issue in a rabbit model, we evaluated in chapter 12, a series of patients with colorectal metastases after PVE and liver resection. Not only the hypertrophy response of the FRL and tumor mass were investigated, but also the outcomes of resection and survival during follow-up.

A conceivable treatment option, to prevent increased tumor growth in patients who have to undergo PVE, is embolization of the hepatic artery branches supplying the tumor-bearing liver segments. In chapter 13, the same VX2 liver tumor rabbit model is used to examine the influence of hepatic arterial embolization on tumor growth and the atrophy/hypertrophy response of the embolized and non-embolized liver lobes, respectively.

Finally in chapter 14, the results of the studies performed in this thesis are summarized and discussed.
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