Clinical and experimental studies on portal vein embolization / Diagnosis of hepatocellular adenoma and focal nodular hyperplasia
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Part I

Summary, conclusions and future perspectives

Clinical and experimental studies on preoperative portal vein embolization
Summary and conclusions

The first part of this thesis concerns liver regeneration after portal vein embolization (PVE). The use of PVE over the past 20 years was reviewed and its effect on tumor growth and (postresectional) hypertrophy response discussed. The effects of several portal vein occlusion techniques were evaluated in experimental studies using a rabbit model of PVE.

Chapter 1 is a historical review of how the concept of portal vein occlusion was defined. As early as in the late 19th century, James Cantlie foresaw that the potential of one half of the liver to hypertrophy when the other half is deprived of its blood supply, could be used to the advantage of hepatic resection. It would take another 85 years, however, before the first clinical, preoperative PVE was carried out.

The use of PVE in the clinical setting over the past 20 years (1990-2011) was reviewed in Chapter 2. After critical evaluation, 44 publications were included for this review comprising 1791 patients. The mean hypertrophy rate of the FRL after PVE was 37.9 ± 0.1%. In 52 patients (2.9%), surgery was not performed because of failure of PVE. Major complications were seen in 2.5% and the mortality rate was 0.1%. A meta-analysis of several subgroups could not be performed because of the small number of articles and the inhomogeneity of the subgroups. However, a head-to-head comparison could be made. In conclusion, preoperative PVE appeared to be an effective method to increase the FRL volume with a high technical and clinical success rate. Pre-existing liver damage due to cirrhosis, cholestasis, or chemotherapy seemed to have no influence on the hypertrophy response. However, the use of n-butyl cyanoacrylate seemed to result in a greater hypertrophy response compared to the other materials used.

In Chapter 3, a retrospective case-control study was performed to assess the effect of preoperative PVE on liver volume and liver function 3 months after major liver resection, as measured by CT volumetry and hepatobiliary scintigraphy. Data were collected of 10 patients who underwent PVE prior to (extended) right hemihepatectomy and of 13 comparable control patients who underwent the same type of resection without prior PVE in the same time period. The future remnant liver volume prior to intervention was significantly less in the PVE group compared to the control group. Prior to surgery (and after PVE in the embolization group) there were no longer significant differences in future remnant liver volume and function between the groups. Three months postoperatively, there were still no significant differences in mean remnant liver volume and function between the groups. The remnant liver regenerated up to approximately 80% of its initial total liver volume and over 83% of its original total liver function, 3 months after major liver resection with or without prior PVE. From this study, we therefore concluded that preoperative...
PVE does not hamper the regenerative capacity of the future remnant liver after partial liver resection.

Chapter 4 discussed several controversies and issues concerning PVE. PVE is considered when the FRL is found to be too small for sufficient postoperative function. However, the criteria for preoperative application of PVE are not well defined. Especially the true minimum volume of liver required for safe resection in a normal liver is debatable, rendering the indication for performing PVE in normal livers controversial. Embolization of the portal branches to segment 4 in addition to embolization of the right portal trunk is controversial and is advised only in selected cases. Clinical and experimental data suggest that tumor progression can occur after preoperative PVE in embolized and nonembolized liver segments, which is a major concern. The regeneration rate of the non-embolized liver segments typically shows an increase during the first 3 weeks after PVE, followed by a plateau phase with only slight additional increase of FRL volume. Therefore a waiting time of 3 weeks between PVE and liver surgery is advised. Finally, PVE does not seem to hamper postresectional liver regeneration.

Chapter 5 is a review of the evidence regarding the effect of PVE on tumor growth. Although clinical studies clearly demonstrated that tumor progression after PVE is possible, accurate data concerning increase of tumor growth rate after PVE were lacking. Three possible mechanisms inducing tumor growth after PVE have been proposed, namely changes in cytokines and growth factors, alteration in hepatic blood supply, and enhanced cellular host response promoting local tumor growth. Sequential TACE with PVE as well as post-PVE chemotherapy were discussed as promising strategies to control tumor progression after PVE.

Chapter 6 describes the development of a rabbit model for PVE to study the hypertrophy response of the liver after this intervention. The combination of two PVA particle sizes and three coils created a PVE model in the rabbit that resembles the human situation, taking into account features as the amount of embolized liver tissue, histologic changes in the liver parenchyma, and the hypertrophy response assessed by CT volumetry. This rabbit model provides an opportunity to perform investigations in a standardized animal model in order to improve the techniques currently used in PVE.

In Chapter 7 the hypertrophy response after portal vein ligation and PVE was compared in the rabbit model. The conclusion was that PVE is superior to PVL in terms of the extent of the hypertrophy response. In the rabbit model, we also compared the use of several embolization materials for PVE in Chapter 8. Polidocanol was discontinued because of toxic reactions in 3
rabbits. Gelatin sponge was the only material that was absorbed within 7 days and this resulted in less hypertrophy of the non-embolized lobe compared to fibrin glue, polyvinyl alcohol particles with coils, and n-butyl cyanoacrylate. No other mechanism than recanalisation of the unilateral portal venous system was found to explain the differences in liver regeneration.

In Chapter 9 the value of hepatic vein embolization (HVE) in addition to PVE was assessed. HVE alone showed no hypertrophy response of the non-embolized liver lobe. A combination of HVE and PVE did not result in a greater or earlier hypertrophy response than PVE alone. The results of this study suggest that simultaneous, unilateral embolization of the hepatic and portal vein is not to be recommended.

**Future perspectives**

Many issues concerning PVE still remain unexplored. A major concern is potential acceleration of tumor growth after PVE. The rabbit model including a tumor engrafted in the liver, will provide the appropriate model to confirm this phenomenon and subsequently, to find solutions to tackle this problem. PVE results in compensatory hyperperfusion of the ipsilateral hepatic artery branch, which promotes growth especially of hypervascular tumors as hepatocellular carcinoma. Sequential embolization of the hepatic artery, feeding the tumor, and embolisation of this artery offers an attractive strategy to limit tumor progression subsequent to PVE. There also is a need for absorbable embolization materials which occlude the portal vein long enough to result in sufficient hypertrophy response, but which are absorbed shortly after occlusion thereby obviating permanent atrophy of the embolized segments.

Finally, the underlying mechanisms of the hypertrophy response after PVE, consisting of a growth factor and cytokine response, need to be unravelled. These issues require further experimental and clinical research in the near future.