Radiological aspects of portal vein embolization
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Chapter 14

Summary, conclusions and future perspectives

K.P. van Lienden
Summary and conclusions

This thesis deals with liver regeneration after portal vein embolization (PVE) or portal vein ligation (PVL). Several aspects of these portal vein occlusion techniques have been evaluated in clinical and experimental studies. In addition, the role of dynamic liver function tests and CT-volumetry in risk assessment before major liver resection has been evaluated in several clinical studies.

After a general introduction in chapter 1, a systematic review was presented of literature over the last 20 years (1990-2011) in chapter 2, describing the clinical use of portal vein embolization (PVE). After critical evaluation, 44 publications were finally included for meta-analysis, consisting of 1791 patients with a mean age of 61 years.

Overall technical success rate was 99.3%. The mean hypertrophy rate of the FRL after PVE was 37.9 ± 0.1%. In 70 patients (3.9%), surgery was not performed because of failure of PVE (clinical success rate 96.1%). In 51 patients (2.8%) the hypertrophy response was insufficient to perform liver resection. In the other 19 cases, 12 were not technically successful (0.7%) and in 7, a complication led to unresectability (0.4%). In 6.1% of patients, resection was cancelled because of local tumor progression after PVE. Major complications were seen in 2.5% and the mortality rate was 0.1%. A meta-analysis of the subgroups could not be performed because of the small numbers of articles or the inhomogeneity of the data. A head-to-head comparison showed a negative effect of liver cirrhosis on hypertrophy response. N-butyl cyanoacrylate seemed to result in a greater hypertrophy response compared to other embolization materials used. No difference in regeneration response was seen in patients with a predamaged liver caused by steatosis, cholestasis or chemotherapy.

Chapter 3 described the outcomes of PVE and extensive resection in patients with a predamaged liver. Between January 2005 and July 2011, 56 consecutive patients underwent successful PVE by percutaneous ipsilateral approach. The mean increase of the FRL was 51% (0-305%). Insufficient hypertrophy response precluding surgical resection was seen in only one patient (1.7%). There were no significant differences in hypertrophy response of FRL after PVE between patients with or without chemotherapy (p=0.51), fibrosis/steatosis (p=0.43) and patients with or without cholestasis (p=0.58). There were no significant differences in regeneration three months after liver resection. It was concluded that PVE is a safe and efficient technique to increase the FRL, also in patients with a predamaged liver.

Assessment of the difference in hypertrophy response between portal vein embolization (PVE) and portal vein ligation (PVL) was described in chapter 4 using a standardized rabbit model. The increase of the unaffected caudal lobe was greater after PVE than after PVL (p = .001), with a mean degree of hypertrophy of 20% ± 2%, and 15% ± 4%, respectively. This was confirmed by Ki-67 staining, which showed a significantly greater number of proliferating hepatocytes after PVE (P = .016). This study proved the superiority of PVE over PVL in a standardized rabbit model.

In chapter 5 intrahepatic vascular changes were studied in patients undergoing PVL or PVE. Between December 2008 and October 2011, 7 patients underwent right PVL and
14 patients PVE. CT-volumetry and $^{99m}$Tc-mebrofinin-HBS was performed in all patients before and 3 weeks after portal occlusion. In 18 patients an intra-operative portography was performed to assess perfusion through the occluded portal branches. In all patients after initially successful PVL, reperfused portal veins were seen on CT scan three weeks after portal vein occlusion. This finding was confirmed in all cases using intra-operative portography. Intrahepatic porto-portal collaterals were identified in all patients in the PVL group and in one patient of the PVE group. Porto-portal collateral flow was seen from segment 4 to segment 5 or 8. The median increase of FRL volume after PVE was $41.6\%$ (range 10-305), and after PVL only $8.1\%$ (range 0-102) ($p=0.179$). Therefore we concluded that PVE and PVL are both useful methods to induce hypertrophy of the FRL before major liver resection. PVL, however, is less efficient in inducing hypertrophy, compared to PVE. This is most likely caused by the formation of intrahepatic porto-portal neo-collateral vessels through which the ligated portal branches are reperfused despite adequate ligation procedure.

Chapter 6 discussed the influence of permanent versus absorbable embolization materials on hypertrophy response after PVE in a rabbit model. The use of Polidocanol was discontinued because of toxic reactions in 3 rabbits. Gelatin sponge was the only material that was absorbed within 7 days resulting in less hypertrophy of the non-embolized lobe compared to the permanent occluding materials (fibrin glue, polyvinyl alcohol particles with coils (PVAc), n-butylcyanoacrylate (nBCA). No other mechanism was found to explain the differences in liver regeneration.

For patients who clinically fail PVE because of insufficient hypertrophy response, alternative methods to optimize the hypertrophy response after portal vein embolization (PVE) are desired. In chapter 7 the effect of hepatic vein embolization (HVE) in addition to PVE on the liver hypertrophy response in a standardized rabbit model was assessed. Although histological and additional regenerative changes were seen, HVE in addition to PVE, caused no greater or earlier hypertrophy response than PVE alone. The combination of HVE and PVE may, therefore, have little use in a clinical setting.

The possibility of performing an extended liver resection is dependent on the volume of the remnant liver. Therefore, preoperative risk assessment is very important. In Chapter 8, future remnant liver (FRL)-function assessed by $^{99m}$Tc-mebrofinin hepatobiliary scintigraphy (HBS) was compared with FRL-volume assessed by CT-volumetry, in the prediction of liver failure after major liver resection.

CT-volumetry and $^{99m}$Tc-mebrofinin-HBS were performed prior to major resection in 55 high-risk patients, including 30 patients with parenchymal liver disease. Liver volume was expressed as percentage of total liver volume or as standardized future remnant liver volume. Receiver operating characteristic (ROC) curve analysis was performed to identify a cut-off value for future remnant liver function in predicting postoperative liver failure. Postoperative liver failure occurred in nine patients. A liver function cut-off value of $2.69\%/\text{min/m}^2$ was calculated by ROC-curve analysis.

$^{99m}$Tc-mebrofinin-HBS demonstrated better sensitivity, specificity, and positive and negative predictive value compared to FRL-volume. Therefore, the technique is valuable to
estimate the risk of postoperative liver failure, especially in patients with uncertain quality of the liver parenchyma. $^{99m}$Tc-mebrofin-HBS proved of more value than CT volumetry.

In chapter 9 the additional value of dynamic $^{99m}$Tc-mebrofin-HBS single photon emission computed tomography (SPECT) for assessment of the 3D segmental liver function and liver functional volume was evaluated. Preoperative CT volumetry and $^{99m}$Tc-mebrofenin HBS with SPECT were performed in 36 patients undergoing liver resection. In 18 patients postoperative scans were performed within 3 days after operation. Dual-head dynamic acquisitions were used to calculate FRL function using anterior and posterior geometric mean (G-mean) datasets. Total and FRL functional liver volumes were measured by SPECT. Because of the anatomical position of the liver, the anterior projection resulted in an underestimation of FRL function in patients undergoing left hemihepatectomy. In patients with normal liver parenchyma, total functional liver volume was comparable to total liver volume measured by CT volumetry, indicating that $^{99m}$Tc-mebrofin HBS is an accurate method to measure hepatic volume. In compromised livers, compared with normal livers, FRL function per cm$^3$ of liver volume was significantly less, and liver function was not distributed homogeneously, with the segments to be resected being relatively more affected. FRL function, measured by a combination of SPECT and dynamic HBS, was able to accurately predict actual postoperative remnant liver function. Therefore the G-mean dataset is recommended for the assessment of hepatic function by dynamic planar $^{99m}$Tc-mebrofin HBS. The combination of SPECT data with the dynamic uptake function measured by planar HBS provides valuable visible and quantitative information regarding segmental liver function and is an accurate measure for FRL function.

The $^{99m}$Tc-mebrofenin SPECT and CT-volumetry was further evaluated in patients who underwent PVE prior to liver resection in chapter 10. In 24 patients scans were performed before and 3–4 weeks after PVE to measure FRL volume, standardized FRL and FRL function. A hypothetical model was used to assess safe resectability after PVE. The limit for safe resection for FRL function was set at an uptake of 2.69 %/min/m$^2$. For FRL volume and standardized FRL, 25 or 40 per cent of total liver volume was used, depending on the presence of underlying liver disease. After PVE, FRL-function increased significantly more than FRL-volume. The correlation between the increase in FRL volume and FRL function was poor. Using the hypothetical model, 7 patients did not achieve a sufficient increase in FRL-function to allow safe resection 3–4 weeks after PVE, compared with 12 and nine patients based on FRL volume and standardized FRL respectively. In conclusion, the increase in FRL-function after PVE is more pronounced than the increase in FRL-volume, suggesting that the necessary waiting time until resection may be shorter than indicated by volumetric parameters.

An increasing number of publications report on progression of tumorgrowth after PVE, causing unresectability. However, the exact mechanisms are still unknown. Chapter 11 described an experimental study using a rabbit hepatic VX2-tumor model. Two weeks after subcapsular implantation of a VX2 carcinoma in the cranial liver lobe, New Zealand White rabbits were allocated to a control group or PVE group (n=5/group). Tumor growth rate (TGR) was increased in both groups, with a significantly larger increase in the PVE-group over
time (day 14: mean 34.4±4.3mL/day vs. control: 24.1±7.2mL/day). This was confirmed by a significantly higher hypertrophy response and proliferation rate in the non-embolized liver lobes of the PVE group. This finding supports the notion that PVE potentially enhances tumor growth, along with regeneration of the non-embolized liver lobe.

This same issue has been evaluated clinically in chapter 12, where 28 patients with colorectal liver metastases (CRLM) who underwent PVE were compared to a non-PVE control group. The tumor growth rate (TGR) was higher after PVE and seven patients (25%) showed new tumor lesions in the FRL after PVE. Patients after PVE also showed a higher rate (42%) of recurrent metastases after resection in the remnant liver at follow-up. The survival was significantly better for non-PVE patients with a 3 and 5 year survival rate of 77% and 60%, respectively, versus 26% and 22% in patients undergoing PVE (p< 0.001). Therefore we concluded that PVE is associated with increased TGR, new tumor in the FRL and recurrent tumor after resection. This corresponds with the outcomes of the experimental study described in chapter 11. Short intervals as well as interval chemotherapy between PVE and resection are therefore advised.

As an alternative treatment option, to prevent tumor growth, the effect of hepatic arterial embolization was studied in chapter 13 in a rabbit VX2-tumor model. Super selective, arterial bland coil embolization caused massive necrosis of the tumor, despite increase of tumor volume on CT-volumetry. Atrophy of the tumor bearing liver lobe was seen after arterial embolization of the tumor with a concomitant hypertrophy response of the non-embolized lobe, despite absence of histological damage of the tumor-surrounding liver parenchyma. Although the exact mechanism was not specifically investigated, it is assumed that the hypertrophy response after arterial embolization is mediated by the same pathways as after PVE. The fact that PVE has a superior hypertrophy response compared to arterial embolization can be explained by its greater effect on overall hepatic blood perfusion. The question remains however, whether the regeneration response of the caudal lobe is caused only by the damage incurred in the tumor after embolization. On basis of the results of this study, this seems highly suggestive.
Future perspectives

Despite the fact that gradually more and more between portal vein embolization and liver regeneration has been unravelled, there are still many issues that need to be further explored, such as the underlying mechanisms of the regeneration response following portal vein occlusion, the influence of pre-existing liver disease on induced liver regeneration, the effect of single arterial embolization on the atrophy-hypertrophy response and the use of absorbable embolization materials in PVE.

The latter issue is not only important in oncological liver surgery in patients with uncertain resectability but could also play a role in living related liver transplantation in case of small-for-size left liver lobes. Further experimental and clinical research on this topic is required.

Acceleration of tumor growth after PVE is a major concern. For this reason, optimizing treatment strategies is of extreme importance. Accurate monitoring of FRL-function is important to shorten the waiting time until resection. $^{99m}$Tc-mebrofenin hepatobiliary scintigraphy with SPECT for the assessment of hepatic function and liver functional volume has proven useful for this purpose.

Also, there is room in existing liver augmenting techniques to be modified to induce a greater hypertrophy response in shorter time. On the other hand, more effective techniques must be developed to prevent increased tumor growth. Single hepatic artery embolization (HAE) appears promising in suppressing tumor growth, however, has limited effect on the hypertrophy response. Only limited experiences have been reported on sequential application of HAE and PVE in patients. The optimal time interval between the two procedures is also unknown. Additional clinical and experimental research, therefore, is required to further exploit this combined treatment technique.

Recent reports demonstrate a marked volumetric response after Yttrium-90 radioembolization of the hemi-liver. This heralds a very promising strategy as this treatment combines local radiation therapy of the tumor with induction of a hypertrophy response of the untreated liver. Further investigation, however, is needed to determine the factors that contribute to this effect.