Postoperative liver (dys)function

SCIENTIFIC AND SOCIETAL IMPACT

Colorectal carcinoma is one of the most common type of cancer worldwide, with approximately 1,3 million new patients annually. Almost half of these patients develop metastases in the liver. Also, annually approximately 700 patients develop primary liver cancer in The Netherlands. Surgical removal (partial hepatectomy) of the tumor offers the best chance of cure.

Failure of liver functions is an important complication and develops in around 9% of patients after partial hepatectomy. A shifted balance between the amount of liver tissue that is removed, and the quality of the remaining liver tissue seems to be the causal factor. Treatment of liver failure solely consists of supporting measures, which causes a mortality of 30% in patients developing liver failure. In this thesis, several determinants of liver failure are investigated. We studied 1) the impact of chemotherapy on complication rates after partial hepatectomy, 2) criteria that can be used in practice as a definition and predictor of postoperative liver failure, and 3) the role of bile salt homeostasis in liver failure and postoperative liver regeneration.

The influence of chemotherapy on outcome after partial hepatectomy

Preoperative chemotherapy is administered to reduces the size of liver tumors, making more patients eligible for a (smaller) resection. However, previous studies showed that chemotherapy also affects healthy liver tissue, which results in an enlarged liver, ascites, and elevation of serum liver enzymes. Microscopically, dilatation of the blood vessels in the liver is seen (sinusoidal dilatation). In chapter 4 we investigated the influence of liver injury on the outcomes after liver resection. Unfortunately, the results from the studies published up to that point could not be compared properly due to different inclusion criteria and outcome measures. We therefore advocate the formulation of uniform inclusion criteria for prospective studies, as well as uniform definitions for outcome measures such as liver failure and biliary leakage. This would provide a fairer and more reliable picture of the results. Preferably, outcome values specifically related to quality of life of the patient are also included in this set of outcomes. Initiatives such as the DHBA (Dutch Hepato Biliary Audit) are valuable for the prospective collection of data and the application of retrospective studies on these datasets because all relevant data for comparison of (treatments of) patients can be collected.

To formulate an answer to the abovementioned question, all researchers from previous studies on chemotherapy-associated liver injury were approached to share their data for analysis. Multiple researchers gave permission, resulting in a large database with data on chemotherapy regimens, surgical procedures, and patient characteristics. After analyses,

we were able to conclude that sinusoidal dilatation and steatohepatitis increase the risk of serious general complications and liver-specific complications (such as liver failure, hemorrhage, and bile leakage) after partial hepatectomy. In contrast, fatty liver (steatosis) is associated with fewer complications after partial hepatectomy. Chemotherapy regimens consisting of solely oxaliplatin were associated with sinusoidal dilatation, whilst the addition of bevacizumab appeared to limit this injury. Given the negative impact of chemotherapy-induced injury on the outcome after liver resection, we recommend evaluating the quality of liver tissue before surgery, for example by ultrasound or MRI. If there is evidence of liver injury, the surgical plan may have to be adjusted or postponed, depending on the expected complications. One can also opt for removal of the tumorous part of the liver without pre-operative chemotherapy, or to adjust the type of chemotherapy regimen. Of course, this should be discussed in a multidisciplinary team meeting (MDO), in which the valued opinions of, among others, surgeon, oncologist and radiotherapist should be considered.

Definitions and predictive values of the present criteria for liver failure

Because liver failure after liver resection is rare but can lead to major consequences if it does occur, it is virtually impossible to set up studies with mortality as an end point after liver resection. That is why we investigated the existing 'surrogate endpoints' (SEP): a laboratory value or physical sign that can act as a predictor of a specific complication, so that for example supportive therapy can be initiated earlier in the postoperative course. In chapter 5 we examined the current existing SEPs for their validity as predictors of liver complication-specific endpoints. Unfortunately, we could not verify the relationship between the surrogate endpoint and the clinical endpoint, which means they cannot be used as a predictor in practice. Subsequently, in chapter 6 a widely used SEP, the peak bilirubin (serum bilirubin >120 µmol/L within 90 days after major liver resection) was investigated as a predictor of liver failure and liver-related mortality. In our patient database, peak bilirubin was found to have a predictive value of only 22.6% on liver-related death after major liver surgery. This means that more than 3 in 4 patients will not die after meeting this criterion, and that a high bilirubin value is not a reason for discontinuation of supportive therapy or an infaust prognosis.

One way to test liver quality before resection is to measure its functional capacity with an endogenous or exogenous test. An important substance involved in metabolizing exogenous components in the body is glutathione (GSH). Amongst other things, GSH is involved in the processing of paracetamol (APAP) and its toxic metabolite. Presumably, after administration of (a high dose of) paracetamol, the amount of GSH in the liver decreases, whilst the amount of ophthalmic acid (OPH) in the blood rises. In chapter 7 we investigated whether plasma ophthalmic acid could be a useful read-out for hepatic

GSH depletion by testing the liver's detoxifying capacity during partial hepatectomy. In this study, patients were repeatedly administered a (safe) dose of paracetamol while part of the liver or pancreas was surgically removed. In both groups, no reduction in the amount of GSH in the liver was seen, nor was there a marked increase in plasma OPH. Unfortunately, no prediction of liver function could be made based on these results. We speculate that, in case of paracetamol overdose, plasma OPH levels may indicate liver injury. It would be relevant to investigate whether these levels are elevated earlier than standard measures such as ALT and AST, and whether they correlate with patient outcome (liver failure, death). In this case, assisted therapy such as hemodialysis could be started earlier in the post-intoxication course to improve outcome.

The role of bile salt metabolism in liver failure and liver regeneration

Previous studies suggest that an imbalance of bile salts has a negative influence on liver regeneration after liver resection. Both a deficiency and a (significant) overload impede liver regeneration and induce liver failure, while a pinch of extra bile salts seems to have an accelerating effect on liver regeneration. In chapter 8 we designed a mouse model in which we investigated the role of bile salts in liver failure. Mice were offered different diets with an increasing amount of bile salts. We witnessed the mice with the highest concentration of bile salts in the diet appearing less well clinically and showing signs of liver failure. We intend to use these diets in the future as a model for liver failure, whereby interventions to prevent liver failure can be tested.

In chapter 9, a potential therapy to prevent liver failure was tested. Obeticholic acid (OCA), a semi-synthetic bile salt (approved as a second-line treatment for a specific liver disease), was administered to mice after which they underwent partial hepatectomy. By administering OCA to mice in low doses, we hypothesized that liver regeneration was accelerated after partial hepatectomy. Unfortunately, no consistent results were obtained on accelerated growth of liver mass after surgery, while gene expression analysis showed that important genes for liver regeneration were activated. We did not find a clear effect on the amount of bile salts in the liver. In our opinion, this indicates that the regeneration mechanism in healthy mice is already optimal after resection of 70% of the liver tissue. However, in daily clinical practice, we regularly deal with people who do not have a healthy liver or a 'straightforward' surgical procedure. Draining bile salts from the body before surgery has been proven to have a negative effect on outcome after liver resection. We suspect that in this situation the administration of, for example, a semi-synthetic bile salt such as OCA accelerates and optimizes liver regeneration. In clinic, this could lead to safer liver resections in patients with a percutaneous drain. The ultimate goal of all interventions is to enable safe surgical procedures in patients with an affected liver, making more patients eligible for a cure, with fewer complications.