SUMMARY
SUMMARY AND FUTURE PERSPECTIVES
SUMMARY

Surgical resection of perihilar cholangiocarcinoma offers a distinct benefit in long-term survival, but it is a complex procedure. The tumour may extend into segmental branches of the bile ducts, or involve the portal vein and/or hepatic artery. Curative-intent resection requires a combined extrahepatic bile duct and partial liver resection, sometimes including a portal vein resection and reconstruction. These extended procedures are associated with a high risk of postoperative mortality, even more so because many patients present with obstructive jaundice. Selecting the optimal treatment in patients with perihilar cholangiocarcinoma is a trade-off between opportunities for long-term survival against the danger of procedural risks: surgery offers a chance for long-term survival or cure, but perioperative complications may cause abrupt death. This thesis aimed to provide recommendations and clinical decision rules for tailored care in patients with resectable perihilar cholangiocarcinoma.

Preoperative biliary drainage

Biliary drainage is often used to treat jaundice prior to surgery: it reduces the risk of postoperative complications such as liver failure and systemic infection. However, biliary drainage can be harmful when complications related to the drainage procedure deteriorate the patient’s condition prior to surgery. Preoperative biliary drainage is mostly initiated with endoscopic drainage, but chapter 1 showed that endoscopic drainage fails to obtain adequate drainage in many patients (38% overall). These patients require additional percutaneous drainage, and are confronted with potential adverse events of the multiple drainage procedures. A clinical decision rule was developed and validated to tailor the use of endoscopic or percutaneous drainage. The study included patients who underwent initial endoscopic drainage, and identified three subgroups that differed in the risk of requiring additional percutaneous drainage. The high-risk group consisted of patients with a total bilirubin level above 150 µmol/L and Bismuth 3a or 4 tumors. These patients have a risk of 62% to require additional percutaneous drainage, so they should be treated with initial percutaneous rather than endoscopic drainage.

In chapter 2, we present a multi-center study protocol to compare endoscopic and percutaneous drainage in a randomized trial (DRAINAGE-trial), with the broader aim to decrease perioperative morbidity and mortality. The study has an ‘all-comers’ design, implying that all patients selected to potentially undergo a major liver resection for perihilar cholangiocarcinoma are eligible for inclusion in the study provided that the biliary system in the future liver remnant is obstructed. Primary outcome measure is the total number of severe preoperative complications between randomization and exploratory laparotomy. The study is designed to detect superiority of percutaneous drainage: a provisional sample size of 106 patients is required to detect a relative decrease of 50% in the number of severe preoperative complications. Secondary outcome measures encompass the success of biliary drainage, quality of life, and postoperative morbidity and mortality.

Chapter 3 is complementary to the first two chapters, as it compares the long-term effects of both drainage methods. The study assessed overall survival, and the incidence of seeding metastases
that potentially influence survival, in patients who underwent endoscopic (n=157) and percutaneous drainage (n=88) and subsequent resection of perihilar cholangiocarcinoma. After adjustment for propensity score, overall survival between the endoscopically and percutaneously drained groups was similar (hazard ratio 1.05). The number of seeding metastases occurring in the laparotomy scar was also similar between the endoscopically and percutaneously drained groups (3% in both groups). No patient had an initial recurrence in percutaneous catheter tracts. These data suggest that percutaneous drainage can safely be used from an oncological viewpoint.

**Preoperative risk assessment in perihilar cholangiocarcinoma**

A new preoperative staging system was developed to predict resectability of perihilar cholangiocarcinoma in chapter 4. A resection was performed in 309 of 501 patients (62%) who underwent exploratory laparotomy, but metastatic or locally advanced disease was found intraoperatively in 192 patients (38%), precluding a resection. Five independent preoperative predictors were found: jaundice, suspected lymph node metastases, Bismuth type, bilateral portal vein involvement, and bilateral hepatic artery involvement. The derived staging system identified 4 classes with resectability rates of 95%, 69%, 50%, and 15%. The staging system also preoperatively predicted survival after surgery: patients in class 4 had postoperative 90-day mortality of 18% and a median survival of only 7 months. Since the probability of a resection in class 4 was very low while the risks associated with surgery were very high, these patients might benefit from palliative instead of surgical therapy. The preoperative staging system can be useful in shared-decision making, and it will permit reliable stratification of patients for clinical trials investigating neo-adjuvant treatment strategies.

The hazards of surgery were further elaborated in a separate risk score predicting postoperative mortality after major liver resection (chapter 5). Postoperative 90-day mortality was 14% in 287 included patients, emphasizing the high risks associated with surgery in perihilar cholangiocarcinoma. The study identified the volume of the future liver remnant (FLR) as an important risk factor. Not only did the FLR volume independently predict postoperative mortality, it was also shown to interact with biliary drainage status: patients with a small FLR volume below 50% benefited from preoperative drainage; by contrast, patients with a large FLR volume above 50% seemed to have no benefit from preoperative drainage. For the latter patients the risk of cholangitis developing after drainage outweighs the questionable benefit of biliary decompression. Therefore, resection in patients without preoperative drainage in the presence of an FLR volume above 50% may reduce postoperative mortality. A mortality risk score based on the analysis had good predictive accuracy. The study identified a low-risk group that should directly proceed to surgery, an intermediate risk-group that may benefit from additional preoperative interventions such as biliary drainage or portal vein embolization, and a high-risk group with an unacceptable risk of surgery. Both prognostic systems in chapter 4 and 5 currently lack validation in an external dataset. However, the derivation datasets included patients from two specialized centers and these combined datasets rank among the largest available.
Preoperative decision-making may be additionally informed by assessment of patient frailty. Chapter 6 investigated the effect of low skeletal muscle mass, as measured on computed tomography images, with regards to short- and long-term outcomes after liver resection for perihilar cholangiocarcinoma. The study showed that low skeletal muscle mass is associated with high postoperative mortality (29% in patients with low skeletal muscle mass versus 9% in patients without low skeletal muscle mass). Furthermore, low skeletal muscle mass was a poor prognostic factor for overall survival after resection (hazard ratio 2.0). Skeletal muscle could thus be valuable in preoperative risk assessment, and enhancing nutritional status preoperatively might improve outcomes postoperatively.

**Intra-operative management of bile duct cancer**

Part three of this thesis provides data for intra-operative decision-making. Chapter 7 is an experimental study in jaundiced rats. It was designed to improve resilience of cholestatic liver against damage from ischemia/reperfusion injury, which is an inevitable side effect of surgery that results from the temporary deprivation of blood supply to the liver. We hypothesized that pretreatment with Atorvastatin would have a protective effect, and tested this hypothesis in a bile duct ligation-based rat model of obstructive jaundice and cholestasis. Atorvastatin or its vehicle control were administered orally once daily during 7 days prior to ischemia induction, or intravenously using a single dose at 24 hours or 30 minutes prior to ischemia induction. Contrary to expectations, Atorvastatin pretreatment was not able to protect jaundiced rats from an overwhelming degree of hepatocellular damage after ischemia/reperfusion. Clinical studies are currently warranted to investigate the role of statin treatment in the protection of patients with normal and steatotic liver against ischemia/reperfusion injury, but in these studies there seems to be no role for jaundiced patients.

Chapter 8 includes patients with gallbladder carcinoma, which is an aggressive disease with a high propensity of recurring after resection. The extrahepatic bile duct may contain micro-metastases at the time of resection, so routine extrahepatic bile duct resection has been proposed as part of a curative-intent resection of gallbladder carcinoma. In this study, 26 patients had undergone a resection of gallbladder carcinoma with preservation of the extrahepatic bile duct. None of these patients developed an isolated recurrence in the region of the extrahepatic bile duct, suggesting that routine EBD resection is of no additional value.

**Postoperative staging in perihilar cholangiocarcinoma**

Chapter 9 describes the recurrence rate and pattern after resection of perihilar cholangiocarcinoma in 306 patients. We demonstrated that patients continue to have recurrences beyond four years follow-up until a plateau is reached at about 8 years; the estimated recurrence rate at 8 years after resection was 76%. The high rate of recurrence up to 8 years may justify prolonged postoperative surveillance, although it remains to be determined whether patients with a recurrence benefit from early detection. Only patients with an isolated initial local recurrence (18%) could have benefited from a more extensive resection or liver transplantation. No patients with lymph node metastases had recurrence-free survival beyond 7 years; so node-positive perihilar cholangiocarcinoma
appears incurable with currently available treatment modalities. Altogether, the high recurrence rate emphasizes the need for adjuvant treatment strategies.

Accurate risk stratification may identify subgroups that could benefit from adjuvant treatment. In that respect, chapter 10 compares the conventional 6th and 7th editions of the American Joint Committee on Cancer staging systems. Although the 7th edition distributed patients more equally across stages, both staging systems were found to have modest prognostic accuracy: the concordance index of both staging systems was 0.59.

A new nomogram for disease-specific survival is proposed in chapter 11. The nomogram was developed from 173 patients and externally validated in 133 patients who underwent curative-intent resection of perihilar cholangiocarcinoma. Lymph node involvement, resection margin status, and tumor differentiation were independent prognostic factors in the derivation dataset. A nomogram with these factors had good prognostic accuracy in the validation dataset (concordance index 0.72), which was better than the American Joint Committee on Cancer staging system. Calibration was suboptimal because disease-specific survival differed between the two institutions. The nomogram can inform patients and physicians, guide shared decision-making for adjuvant therapy, and stratify patients in future randomized controlled trials.

Chapter 12 describes the prognostic value of micrometastases detected on immunohistochemistry. Micrometastases were identified in 11 of 91 patients (12%) who had node-negative perihilar cholangiocarcinoma on routine histology. Five-year survival rates in patients with lymph node micrometastases were significantly lower compared to patients without micrometastases (27% versus 54%), and multivariable analysis confirmed micrometastases as an independent poor prognostic factor for survival (hazard ratio 2.4). Lymph node micrometastases were shown to be a stronger predictor than resection margin status, and comparable to lymph node metastases found on routine histology. Incorporating micrometastases in staging systems may thus improve their prognostic accuracy.

Chapter 13 presents a meta-analysis that compares immunohistochemical biomarker expression profiles between resected intrahepatic and extrahepatic cholangiocarcinoma. The study found a different expression in 18 of the 57 markers that were evaluated in a total of 4458 patients, which is especially relevant in markers that are potential targets of molecular therapy (EGFR, c-erbB-2 and VEGF-A). These results corroborate earlier findings that intrahepatic and extrahepatic cholangiocarcinoma are distinct forms of cancer. As a consequence, these subgroups should be separated when therapies targeting tumor biology are being considered. The subject of this thesis, perihilar cholangiocarcinoma, constitutes a mixed group of intrahepatic and extrahepatic tumors around the liver hilum, but after all, this mixed group will need to be subclassified in future treatment algorithms.
FUTURE PERSPECTIVES

Several important topics regarding resectable perihilar cholangiocarcinoma are currently under investigation. Most research projects in the past have been limited to retrospective studies, but multi-center and international collaborations are evolving and will provide a basis for randomized trials in the future. The DRAINAGE-trial, as described in this thesis, compares endoscopic and percutaneous preoperative drainage. The study is designed to identify the method associated with the fewest complications and lowest perioperative mortality. After completion of this study, the next question that should be addressed is whether preoperative drainage is beneficial at all. The use of routine preoperative drainage for resection of cancer of the pancreatic head has recently been abandoned, since it was shown to increase the rate of perioperative complications. This thesis suggests that patients with perihilar cholangiocarcinoma and a future liver remnant volume above 50% neither benefit from preoperative drainage, corroborating findings from other recent studies. Based on these studies, a randomized trial is needed to assess if resection without preoperative drainage in the presence of a sufficient future liver remnant volume reduces perioperative morbidity and mortality.

Other interventions to reduce perioperative morbidity and mortality in patients with perihilar cholangiocarcinoma might involve pharmacological agents. One of the potential targets is bile salt homeostasis, which has recently been identified as a key regulator in recovery from liver injury. Experimental studies in rats showed that bile salt-activated transcription factor FXR (farnesoid X receptor) is required for normal liver regeneration, and that the FXR-induced enterokine FGF15 (Fibroblast Growth Factor 15, termed FGF19 in humans) has an important role in the negative feedback loop of bile salt synthesis. Modulating FXR and FGF19 seems especially relevant for patients with perihilar cholangiocarcinoma, who often have perturbed bile salt homeostasis due to obstructive jaundice and cholestasis. FXR activation with synthetic bile acids was shown to protect the liver from cholestasis, and above all, FXR and FGF19 agonists may improve liver regeneration after resection. Clinical studies will hopefully follow soon after preclinical studies have tested such agents.

The risk scores predicting resectability and postoperative mortality in this thesis showed good prognostic accuracy, but require external validation before they can be applied clinically. Future validation studies should also include the recently developed staging system from Mayo clinics, and the comprehensive staging system described by DeOliviera et al. The rare incidence of the disease demands international registries to obtain adequate numbers of patients; only studies including patients from multiple centers are able to reach sufficient statistical power.

Similar to other gastro-intestinal cancers, adjuvant treatment is anticipated to offer a distinct survival benefit after resection of perihilar cholangiocarcinoma. Three international studies are currently investigating adjuvant treatment after resection of cholangiocarcinoma. (clinicaltrials.gov identifiers: NCT00363584, NCT01313377, and NCT02170090). Study designs under investigation
include capecitabine versus observation, gemcitabine plus oxaliplatin versus observation, and gemcitabine plus cisplatin versus observation. The latter design is based on the only phase III clinical trial that showed a survival benefit in palliative treatment of cholangiocarcinoma.\textsuperscript{13} The study is currently enrolling patients in 5 countries, including the Netherlands.\textsuperscript{14} At present, targeted molecular therapies and immune-modulating therapies are not available for cholangiocarcinoma, but these therapies might be able to further improve survival after resection in the future.\textsuperscript{15-17}
REFERENCES

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