Tailored care in resectable perihilar cholangiocarcinoma
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GENERAL INTRODUCTION
AND OUTLINE OF THE THESIS
BACKGROUND

Cholangiocarcinoma is a rare form of adenocarcinoma that originates in the epithelial cells of the bile ducts. It has an estimated incidence of 5 patients per 100,000 inhabitants in Western countries, accounting for less than 2% of all human malignancies, but the incidence is rapidly increasing. Usual classifications distinguish tumors arising from bile ducts inside or outside the liver, i.e. intrahepatic and extrahepatic cholangiocarcinoma. Yet, the border of the intrahepatic and extrahepatic bile ducts, which is located near the confluence of the bile ducts in the liver hilum, is the most frequently involved site. Cholangiocarcinoma tumors arising at this location vary in their intrahepatic or extrahepatic origin, and constitute several morphological subtypes, including mass-forming, periductal, and intraductal tumors. Nonetheless, these tumors share similar features on cholangiography, require similar surgical management, and are associated with comparable survival. Therefore, the American Joint Committee on Cancer staging system groups these tumors together as ‘perihilar cholangiocarcinoma’ – the name being a testimony to their origin in the bile ducts around the liver hilum. (Figure 1) The group of perihilar cholangiocarcinoma includes tumors originating in the hepatic duct, the hepatic duct confluence, and in the left or right hepatic duct. These tumors have previously been described as ‘hilar cholangiocarcinoma’ or ‘Klatskin tumors’, but these names failed to capture the mixture of intrahepatic and extrahepatic tumors. Perihilar cholangiocarcinoma is the most frequent subtype of cholangiocarcinoma with an incidence of 1 to 2 patients per 100,000 inhabitants, and is the major focus of this thesis.

Figure 1. Diagram showing the groups of bile ducts that cholangiocarcinoma can arise from. Image used with permission from Cancer Research UK / Wikimedia Commons.
TREATMENT

Perihilar cholangiocarcinoma in early stage are mostly indolent growing tumors, progressing slowly without being noticed by the patient. Tumors can grow proximally into the biliary tree, where they form a complex relation with the segmental bile ducts. To characterize this involvement, the proximal extent of perihilar cholangiocarcinoma is described using the Bismuth classification, which was originally designed in 1975 by Henry Bismuth and Marvin B. Corlette.\(^6\) Jaundice is often the first clinical symptom – it develops after the tumour obstructs the bile ducts fully and the patient’s blood begins to fill up with bile pigments. The majority of tumors has critically invaded the local vasculature by then, or has metastasized to distant sites in the body. Therapy in patients with locally advanced or metastatic disease is limited to palliative chemotherapy, and the reported median survival is only 12 months.\(^7\) Surgical resection, however, is a viable option in patients with tumors detected at earlier stage. Localized perihilar cholangiocarcinoma are effectively treated by resecting the extrahepatic bile duct and part of the liver, which is sometimes combined with a portal vein resection and reconstruction if necessary. Data from the Dutch registry (Nederlandse Kanker Registratie) showed that approximately 10% of patients diagnosed with perihilar cholangiocarcinoma between 2009 and 2011 underwent a resection.\(^8\) The median survival reported after resection varies between 30 and 40 months,\(^9\) rendering surgery favorable over any other type of treatment. Moreover, survival after surgery has been improved in recent years since the deployment of multidisciplinary teams and the introduction of extended resections.\(^12\) Combined resection including a bile duct resection and a hemihepatectomy (at least three segments of the liver) has been shown to prolong survival compared to a local bile duct resection only, and it is now considered the gold standard in treatment of perihilar cholangiocarcinoma.

HAZARDS IN SURGERY

Despite the favorable role of surgery, it also entails severe hazards. Staging of perihilar cholangiocarcinoma is complex due to possible involvement of the segmental biliary tree and local vascular structures. Computed tomography (CT) and/or magnetic resonance cholangiopancreatography (MRCP) are used to assess resectability, but have imperfect accuracy to detect locally advanced tumors or metastasis.\(^13\) As a result, approximately 40% of patients undergoing exploratory laparotomy are ultimately diagnosed with unresectable disease during the operative procedure – occult metastases are recovered or the tumor appears to critically invade local vascular structures. A resection cannot be performed in these patients, but the aftermath of a negative procedure may still result in postoperative complications such as pneumonia or wound infection, hampering physical status and quality of life. Surgery without resection confronts patients with potential adverse events, whilst offering no survival benefit.

Hazards in patients who undergo an actual resection of perihilar cholangiocarcinoma are even larger. Most of these hazards are caused by jaundice, which has detrimental effects on the patients’ physical status: Jaundice reduces the function as well as regenerative capacity of the liver due to
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cholestasis; it impairs nutritional status by deviating bile from the gastro-intestinal tract; and it predisposes patients to infection due to a portal and systemic bacterial translocation from the gut. These changes have far-reaching consequences. Not only does jaundice impact patients’ quality of life, it also sensitizes the patient to surgical injury – already in 1935, Allen Whipple acknowledged an increased risk of surgery in jaundiced patients. Especially in the setting of combined bile duct and partial liver resection, jaundiced patients are at high risk of postoperative morbidity and mortality. Observed complications include, but are not limited to: liver failure, bile leakage from the hepaticojejunoanastomosis, abscess formation, and sepsis. These complications culminate in a postoperative mortality rate that is reported between 5 and 18%, qualifying liver surgery for perihilar cholangiocarcinoma among the most dangerous surgical procedures performed nowadays.

Figure 2. The Bismuth classification describes the proximal extent of the tumor. Type 1 grows below the confluence of the left and right hepatic ducts; type 2 involves the confluence; type 3A and 3B grow into the right and left segmental hepatic ducts, respectively, and type 4 grows into the segmental hepatic ducts bilaterally.

TAILORED CARE

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 the only chance for long-term survival or cure, but perioperative complications may cause abrupt death. Choices need to be made in several stages of the perioperative process, which are summarized in Figure 3. The challenge is to select the optimal treatment in each of these stages, whilst unacceptable risks are avoided: tailored care is at the heart of the matter.
**AIMS**

Many types of gastro-intestinal cancer have seen tailored care introduced a long time ago, but a lack of data have limited its introduction in treatment of cholangiocarcinoma. The rarity of the disease limited the development of adequate prognostic models, let alone the validation of any kind of model. For the present thesis, multi-institutional collaborations were sought to improve statistical power: many patients were included from the Academic Medical Center in Amsterdam, the Memorial Sloan Kettering Cancer Center in New York, and the University Medical Center Groningen. These collaborations have resulted in a series of studies that evaluated prognostic factors, developed new prognostic models, and validated existing models. The aim of this thesis is to provide recommendations and clinical decision rules for tailored care in patients with resectable perihilar cholangiocarcinoma. The broader objective is to improve patient selection for surgery and additional interventions, as well as to increase perioperative safety.

**OUTLINE OF THE THESIS**

The first part of this thesis focuses on biliary drainage, which is used to treat jaundice prior to surgery. Preoperative biliary drainage creates a passage for bile along an obstructing tumor; it reduces cholestasis and it restores the enterohepatic circulation of bile acids. These properties decrease 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. Especially cholangitis developing after biliary
drainage is a notorious risk factor with regards to perioperative mortality. In order to decrease the risk of complications, biliary drainage is thus required to be effective and performed using as few procedures as possible. Two methods of biliary drainage are available, including endoscopic and percutaneous drainage, and both methods possess benefits and risks. Chapter 1 provides a clinical decision rule to choose the appropriate method based on the patient’s profile, since extensive tumor involvement and high bilirubin levels were shown to predict failure of endoscopic drainage. In chapter 2, we present a study protocol to compare endoscopic and percutaneous drainage in a randomized trial. The study is designed to identify a difference in the total number of severe preoperative complications, with the broader aim to decrease perioperative morbidity and mortality. Chapter 3 is complementary to the first two chapters, as it compares the long-term effects of both drainage methods.

The second part of this thesis contemplates preoperative risk assessment. Staging systems are needed to inform patients and physicians preoperatively of the potential benefits and risks of surgery. Ideally, such staging systems are able to enhance shared-decision making shortly after diagnosis of the disease: Chapter 4 provides a new preoperative staging system that may be used to select patients for exploratory laparotomy. The staging system distinguishes four patient categories with incremental chances of resectability and long-term survival. The surgical risks of liver resection for perihilar cholangiocarcinoma are further detailed in chapter 5 that presents a preoperative risk score to predict postoperative mortality. The risk score revolves around the volume of the future liver remnant as one of the most important determinants of surgical risks, and accordingly identifies opportunities to tailor the use of preoperative biliary drainage.

Preoperative decision-making may be additionally informed by assessment of patient frailty, which has been an increasing topic of interest in many research fields. In chapter 6, we used computed tomography to assess preoperative skeletal muscle loss and predict outcomes following partial hepatectomy.

Part three of this thesis provides data for intra-operative decision-making. Chapter 7 is an experimental study that was designed to improve resilience of jaundiced rats 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. Obstructive jaundice from a tumor causes bile acids to accumulate in the liver – a process called cholestasis. Unfortunately, these high levels of bile acids sensitize the liver to ischemia/reperfusion injury. Based on previous studies with statins in rats with normal and fatty livers, we hypothesized that Atorvastatin treatment would also protect the liver in jaundiced rats with cholestatic liver.

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, since it is the neighboring anatomical structure. Therefore, routine extrahepatic bile duct resection has been proposed as part of a curative-intent resection of gallbladder carcinoma,
denying the additional risks associated with such an extended procedure. Our study investigated recurrence patterns after resection of gallbladder carcinoma, and provides new evidence that routine extrahepatic bile duct resection is of no additional value.

Part four considers postoperative staging and implications for adjuvant treatment in perihilar cholangiocarcinoma. Ever since the first study of adjuvant therapy in breast cancer was published in 1981, researchers have been trying to improve survival after resection of all sorts of malignancies. Many phase II studies have been undertaken to test adjuvant chemotherapy in cholangiocarcinoma, but there are currently no randomized trials available to establish the role that adjuvant treatment should have. Based on this lack of clinical trials, Dutch guidelines currently do not approve adjuvant treatment. Nonetheless, a recent meta-analysis of retrospective studies supported adjuvant treatment for cholangiocarcinoma. The study especially found a survival benefit in patients with risk factors for recurrences, such as local lymph node metastasis (N1) or a resection margin with microscopic tumor cells (R1). For the last part of this thesis, we envisioned the installment of adjuvant treatment when results from randomized trials will become available – postoperative risk stratification and patient selection for adjuvant treatment is already evolving as a topic of interest.

Chapter 9 describes the recurrence rate and pattern of perihilar cholangiocarcinoma after curative-intent resection. The study provides important insight into the biological behavior of the disease: many patients develop a recurrence, but these recurrences grow slowly and may manifest only years after resection. The findings in this study emphasize the need for risk stratification and adjuvant strategies after resection of perihilar cholangiocarcinoma. 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 inadequate prognostic accuracy to discriminate between low-risk and high-risk patients after resection. Therefore, we developed and externally validated a new nomogram to predict survival after resection of perihilar cholangiocarcinoma in chapter 11. The nomogram is based on the prognostic factors lymph node status, resection margin status, and tumor differentiation, and may be used to guide shared decision-making for adjuvant therapy in the future. Chapter 12 assessed the additional prognostic value of measuring micro metastases in lymph nodes.

Ultimately, cholangiocarcinoma should be treated with molecular agents targeting specific tumour characteristics, as previously shown effective e.g. with receptor-targeted therapy in breast and colorectal cancer. Chapter 13 describes a meta-analysis that compares immunohistochemical biomarker expression profiles between resected intrahepatic and extrahepatic cholangiocarcinoma. The study aimed to identify avenues for targeted molecular therapy, as tailored care will continue to develop in treatment of cholangiocarcinoma.
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REFERENCES

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