Exploring new strategies in diagnosis and treatment of hilar cholangiocarcinoma
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Chapter 1

General Introduction and Outline of the Thesis
Chapter 1

BACKGROUND

Cholangiocarcinoma is a rare malignancy originating from the epithelial cells of the bile ducts. The age-standardized incidence rate of cholangiocarcinoma in Western countries ranges from 0.5 – 1.5 per 100,000 person-years.\(^1\) Cholangiocarcinoma can arise anywhere along the biliary tree. The American Joint Committee on Cancer distinguishes three types of cholangiocarcinoma based on its anatomic location and developed three separate staging systems: intrahepatic, perihilar (hilar) and distal cholangiocarcinoma.\(^2\) (Figure 1 in chapter 2). This classification is important because at each level the tumor has distinct morphological features and often requires a different surgical approach.\(^3,4\) Hilar cholangiocarcinoma is the most frequent type of cholangiocarcinoma, accounting for 60-70\% of cases, followed by distal (20-30\%) and intrahepatic tumors (5-10\%).\(^5\) It is difficult to provide accurate epidemiological data for the different types of cholangiocarcinoma because the second version of the International Classification of Diseases for Oncology (ICD-O) has misclassified hilar cholangiocarcinoma as intrahepatic instead of extrahepatic tumors. However, it is clear that the overall incidence of cholangiocarcinoma is rising worldwide.\(^6\)

Cholangiocarcinoma exhibits three basic growth patterns: (a) mass-forming, (b) sclerosing, also known as periductal infiltrating, or (c) intraductal growing. Recently, much progress has been made in the study of premalignant cholangiocarcinoma lesions.\(^7\) It has been demonstrated that pre-invasive lesions such as biliary intra-epithelial neoplasm (BilIN), intraductal papillary neoplasm of the bile duct (IPNB), and mucinous cystic neoplasm (MCN) are important for the development and progression of sclerosing and intraductal growing cholangiocarcinoma. These premalignant lesions are found in the intrahepatic and extrahepatic bile ducts and, in the case of BilIN, also in the peribiliary glands. A pre-invasive lesion of intrahepatic mass-forming cholangiocarcinoma has not yet been found. However, there are indications that stem cells/hepatic progenitor cells are involved in the tumorigenesis of some types of intrahepatic cholangiocarcinoma.\(^8\)

Cholangiocarcinoma can remain unnoticed for a long period of time. Intrahepatic tumors may become apparent when tumors reach a certain size producing right upper quadrant pain but can also be found incidentally during medical investigation. Hilar and distal tumors cause symptoms when the biliary flow is obstructed resulting in jaundice or cholangitis. When patients present with symptoms, the medical team is put to the task to confirm the diagnosis and propose a treatment. Intrahepatic and distal tumors are usually diagnosed by
percutaneous or endoscopic biopsies and the treatment consists of resection of the affected liver lobes or pancreatoduodenectomy respectively. Hilar cholangiocarcinoma however, is known for its difficult diagnosis and treatment. Therefore, the focus of the thesis is on hilar cholangiocarcinoma.

Hilar cholangiocarcinoma arises at the confluence of left and right hepatic duct. The
proximal extent of the disease is classified according to Bismuth-Corlette, originally described by Henri Bismuth and Marvin Corlette in 1975.\textsuperscript{9} (Figure 1).

Hilar cholangiocarcinoma is usually not a bulky tumor but infiltrates the bile duct wall longitudinally (sclerosing, periductal-infiltrating type). It extends along the mucosa and submucosal spaces with perineural, lymphatic and vascular infiltration.\textsuperscript{3,11} The tumor appears on endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP) as an irregular stricture. Obtaining pathological confirmation of the disease is difficult because of an intense desmoplastic reaction (fibrosis) around the tumor, resulting in negative endoscopic biopsies.

The only curative treatment for hilar cholangiocarcinoma is radical surgical resection consisting of extrahepatic bile duct resection with partial liver resection. In case of involvement of vascular structures within the hepatoduodenal ligament, the procedure can be combined with hepatic artery or portal vein resection and reconstruction. These are major procedures accompanied by high morbidity and mortality rates. To decrease the risk of postoperative liver failure, percutaneous portal vein embolization of the branch supplying the side of the tumor can be performed to induce hypertrophy of the future liver remnant. Another technique that uses the regenerative capacity of the liver is the ALPPS procedure (Associated Liver Partition and Portal vein ligation for Staged hepatectomy) in which a two-staged hepatectomy is performed.\textsuperscript{12} During the first stage, the liver parenchyma is transected along the intended line of resection together with portal vein ligation of the liver segments containing the tumor. After 1-2 weeks, hypertrophy of the future liver remnant has occurred and the deportalized right hemiliver is removed.

Despite the tendency towards more extended resections to achieve negative margins, overall survival after potentially curative resection is about 38 months.\textsuperscript{13}

Surgical resection of hilar cholangiocarcinoma is precluded in patients with locally advanced disease or when the tumor arises in the setting of an underlying parenchymal liver disease. Recently, liver transplantation for unresectable hilar cholangiocarcinoma has regained attention. Liver transplantation offers wide resection margins and cures an underlying liver disease. The Mayo Clinic group in Minnesota, USA, has pioneered this field by constructing a neo-adjuvant chemoradiation protocol, followed by explorative laparotomy and, in the absence of metastases, liver transplantation.\textsuperscript{14} Inclusion criteria are strict, resulting in a relatively small group of patients that may benefit from this ultimate treatment option.
AIM
Diagnosis and treatment of hilar cholangiocarcinoma remain an enormous challenge for the medical team. Rapid developments are hampered by the fact that the disease is relatively rare. Even high-volume centers usually see only 10-20 new cases per year. Continuous efforts should be made to optimize the diagnostic and treatment process. This thesis explores new strategies that are emerging in the clinical course of hilar cholangiocarcinoma with the aim to improve early diagnosis, staging of disease and appropriate treatment.

OUTLINE OF THIS THESIS
In chapter 2 a concise review on diagnosis and treatment of the entire spectrum of cholangiocarcinoma is presented, including the position of hilar cholangiocarcinoma within this spectrum. In chapter 3 the search for a suitable marker for near-infrared optical imaging of hilar cholangiocarcinoma is described to facilitate earlier diagnosis. In chapter 4 the impact of lymph node micrometasteses is investigated in order to improve postoperative staging.

Frozen section analysis is used during surgery to obtain diagnosis and tumor free resection margins. In chapter 5 the value of intra-operative frozen section analysis is assessed to improve intraoperative decision making. In chapter 6 the vascular complications arising after liver transplantation for hilar cholangiocarcinoma in patients that underwent neo-adjuvant chemoradiation therapy at the Mayo Clinic are described to improve the awareness of the hazards of this intense neo-adjuvant treatment protocol in this group of patients.

Since the Mayo Clinic reported the first results of liver transplantation after neo-adjuvant chemoradiation for hilar cholangiocarcinoma, the question has emerged to what extent the strict selection criteria that are being applied to enter the protocol contribute to the favorable results.

Chapter 7 investigates the results of a of European subgroup of patients comparable to the Mayo Clinic experience - with the exception that neo-adjuvant therapy was not used - to assess the value of selection alone on the outcome of liver transplantation for hilar cholangiocarcinoma.

In chapter 8 the previous chapters are summarized and discussed and future perspectives are provided.
REFERENCES


