Surgical strategies in the management of hilar cholangiocarcinoma
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CHAPTER 1

General introduction and outline of the thesis
General Introduction

Incidence

Cholangiocarcinoma can arise along the entire intrahepatic and extrahepatic biliary tract. Approximately between 2250 and 4500 new cases of cholangiocarcinoma are reported each year in the United States. In large autopsy series the incidence varied from 0.01% to 0.5%. The hepatic duct bifurcation is the site most often involved, and approximately 60% to 80% of cholangiocarcinomas encountered at tertiary referral centers are found in the perihilar region.

Classification

Altemeier et al. first reported 3 cases of primary adenocarcinoma of the perihilar region in 1957. In 1965 however, Gerald Klatskin (Connecticut, USA), described distinctive clinical and pathologic features of this tumor at the hepatic duct bifurcation, and due to the subsequent interest in this tumor, it came to be called Klatskin's tumor. In 1975, Bismuth and Corlette divided hilar cholangiocarcinoma into 4 types, according to the anatomic localization of the tumor at the biliary ducts. A modification was made 17 years later. This classification, which is generally based on ultrasonic- and cholangiographic-findings or macroscopic pathologic appearances at operation, is most frequently used to determine further treatment. In type I tumors, the primary hepatic duct confluence is not obstructed. In type II tumors, the obstruction is limited to the primary hepatic duct confluence and does not extend beyond the left or right hepatic duct. In type III tumors, the primary confluence is obstructed with tumor extension into the right (A) or left (B) secondary biliary radicals. In type IV tumors, the right and left secondary biliary radicals are both involved.

Clinical presentation/ Radiological evaluation

The lesion is usually slow growing and metastases are uncommon, however the diagnosis is usually not made until the bile duct is occluded and the patient is jaundiced.
Patients seldom suffer from pain, and therefore in every patient with signs of painless biliary obstruction, this diagnosis should be considered. During subsequent radiologic evaluation, abdominal ultrasound (US) or CT scan are most often used, showing dilated intrahepatic biliary ducts, a normal or collapsed gallbladder and normal extrahepatic biliary ducts. The tumor mass itself is often difficult to visualize on standard CT scan or US. More recent studies on US however, demonstrated the primary tumor in more than 85% of the patients. The tumors are most often small (mean size of 2.7 cm) and iso-echoic to hepatic parenchyma. It can be difficult to distinguish these tumors from benign lesions. In selective cases, sonographic findings are found to be different. When there is nodular mural thickening, inflammation should be considered. Even infiltrative lesions however, can mimic sclerosing cholangitis. The combination of US with Duplex ultrasound is used to identify possible tumor invasion into surrounding vascular structures.

During further assessment, cholangiography by either endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC), will greatly contribute to the diagnosis and classification. A focal, irregular and eccentric pattern and/or blunt ending is highly suggestive for cholangiocarcinoma. However, although sclerosing cholangiocarcinoma is the most common cause of focal hilar obstruction, many other causes, including several benign lesions, have been recognized and differentiation between these diagnoses is difficult.

**Biliary drainage**

Many authors claim that (bilateral) PTC is preferable above ERCP for high bile duct lesions, in which complete obstruction may prevent proximal visualization by ERCP. However, ERCP with balloon occlusion and (forceful) contrast injection can also fill the proximal biliary tree and thus, can often be helpful to determine the proximal extent of the tumor and thereby resectability. During both procedures, bacterial flora in the bile ducts is being altered, which increases the risks of resistant nosocomial infection and may be associated with increased mortality and morbidity rates after resection or pallia-
Even before any instrumental contamination could have occurred, the biliary tree appeared to be contaminated in as many as 36% of cases. Therefore, biliary drainage by placement of endoprostheses or transhepatic catheters, is found necessary and can be achieved during both procedures. Randomized studies however, did not support the role of preoperative drainage to reduce operative mortality. On the contrary, the use of one or more stents during biliary drainage, in patients with a cholangiocarcinoma, may even have adverse side-effects. Perturbation of the tumor can cause tumor cells to detach. Contamination of bile with malignant cells can result in tumor spill during resection and subsequent reconstruction of the biliary-enteric system, with the potential hazard of occurrence of implantation metastases in the operative field.

Assessment of resectability

In 1992, laparoscopy with ultrasonography has been introduced in our institution for evaluation of operability in patients with proximal bile duct tumor. In 40% of patients with proximal bile duct tumors, unnecessary explorative laparotomies could be avoided. The additional value of ultrasonography during laparoscopy, was however limited. Application of other diagnostic methods in hilar cholangiocarcinoma, such as endosonography and cholangioscopy have been described but, due to its operator dependency, are not standard procedures in most referral centers. More recent results of thin-section multiphasic spiral CT scan and MRCP seem to be more promising.

Biopsy/ cytology/ tumor markers

Preoperative tissue diagnosis by fine-needle aspiration biopsy, brush biopsy during cholangiography or cytologic examination of bile is not considered to be essential, especially when surgery is planned. Bile obtained from a percutaneous catheter demonstrates malignant cells in only 30% of cases, which can be improved to 40% by brush cytologic studies, and to 67% by fine-needle aspiration. Therefore, a negative brush or cytology study does not exclude malignancy and because also false-positive brushes have been found after
previous stenting, cytologic studies have limited impact on treatment strategy.

The use of tumor markers during diagnostic assessment of hilar cholangiocarcinoma seems to be limited because they are not specific and may also be present under non-malignant conditions. However, cancer antigen (CA) 19-9 is currently widely used, in particular for detecting cholangiocarcinoma in patients with primary sclerosing cholangitis and also increased levels of CEA in bile have been reported in patients with cholangiocarcinoma.

**Surgical resection**

The aim of surgical treatment in hilar cholangiocarcinoma is twofold: reestablishment of biliary drainage and local control by eradication of the tumor. Depending on the extent of the tumor, these objectives can be obtained either by local resection of the hepatic duct confluence together with the tumor mass, or by hilar resection in combination with major liver resection. In our institution, in addition to the judgement of the patient's overall medical condition, the lesion is considered for resection, during both preoperative assessment and subsequent operative exploration, when peritoneal or distant metastatic involvement is absent, and when there are no signs of local tumor progression. Local irresectability is hereby defined as bilateral tumor extension into the segmental intrahepatic bile ducts (Bismuth type IV tumor), or tumor invasion into left and right branches or the main trunk of the portal vein and/or hepatic artery, or tumor invasion into a portal vein and/or hepatic artery branch combined with tumor extension into segmental bile ducts of the contralateral liver lobe.

Generally, the following procedures for each type of lesion are recommended: local resection of the confluence area in type I tumors and local resection combined with resection of segment I (caudate lobe) in type II tumors. The technique of local resection basically consists of division of the common bile duct at its entry of the pancreas and posterior dissection of the bile duct in cephalad direction up to the hilum. At this point, the dissection is continued intrahepatically proximal of the confluence and the bile ducts are resected above the tumor. The resection margins are checked for residual...
tumor by frozen section examinations. For biliary reconstruction, two or more hepatico-jejunostomies are created using a Roux-en-Y jejunal limb.

For tumors extending into the right (IIIa) or left (IIIb) segmental ducts, respectively, a right or left hemihepatectomy, often including the caudate lobe has to be performed.\textsuperscript{47,52} During a right hemihepatectomy, extension of the resection with the extirpation of segment IV, will facilitate the procedure and is therefore commonly performed in our institution. Biliary drainage of the residual liver is completed via intrahepatic cholangio-jejunostomies between segmental hepatic ducts, which are often sutured together, and a Roux-en-Y jejunal loop. In type IV tumors, Bismuth et al. recommended total hepatectomy plus liver transplantation.\textsuperscript{9} Previous studies have not shown that liver transplantation has substantial benefit in the treatment of extended hilar cholangiocarcinoma, and in our institution, palliation is generally performed in these cases.\textsuperscript{53-55} In recent series from Japan, the USA and Germany, however, in case of advanced hilar cholangiocarcinoma, the highest surgical radicality is claimed after liver transplantation, resulting in satisfactory long-term survival.\textsuperscript{56-59}

Postoperative complications

As a result of these extensive procedures, postoperative complication rates are high, including complications as: bile leakage, liver failure, sepsis/cholangitis, intra-abdominal abscesses and postoperative or gastro-intestinal bleeding.\textsuperscript{1,4,52,56-61} The overall morbidity rate in most recently published reports varied between 22\% and 54\% for local resections and liver resections, respectively.\textsuperscript{4,9,50,52,61-64} A 30-days mortality of 14\% for local resections and 22\% for liver resections has been reported before 1980, whereas between 1980 and 1989, these rates decreased to 8\% and 15\% respectively.\textsuperscript{65} More recently, a mortality rate of 8\% after hepatic resections has been reported.\textsuperscript{1} The advantage of local excision obviously is the lesser procedure compared to the more complex, extended resections which are associated with higher operative morbidity and mortality rates. Whether this lesser procedure results in complete tumor clearance, on the other hand, is a major concern.\textsuperscript{52}
Resection margins

Despite the fact that the tumor usually is small, it has close relations with important local structures in the hilum of the liver, such as the hepatic artery and portal vein, and often there is progression along the proximal biliary system with perineural and lymphatic involvement. Therefore, to achieve a margin-negative resection is technically demanding and often impossible. In recent series, resectability rates among patients operated for hilar cholangiocarcinoma varied among 50-97%, with margin-negative resections reported between 11 and 78%. However, examination of surgical resection planes alone, in these studies, probably did not provide adequate information for complete surgical extirpation of these tumors. Surgical dissection (cleavage) planes should also be taken into consideration. Extensive pathological examination of these planes, may explain the lower rate of 'radical', resections, as previously reported from our institution. And, although several studies have concluded that in the treatment of hilar cholangiocarcinoma, radical excision of the lesion still offers the best treatment option with respect to long-term survival, survival results from our institution were comparable with the literature. In view of this controversy, possible other unknown factors determining long-term survival have to be discovered.

Radiotherapy

There is no consensus about the use of perioperative radiotherapy in patients with resectable hilar cholangiocarcinoma. Preoperative radiotherapy proved to be effective in preventing scar implants after surgical treatment of bladder cancer, by decreasing viability of cells shed by the tumor. In a previous study, cytologic examination of bile obtained during surgery from intrahepatic bile ducts, in patients with malignant proximal bile duct obstruction, has shown a high incidence of tumor cells. Spill of bile occurs frequently during resection and to diminish the implant ability of spilled tumor cells, Buskirk et al. suggested also low-dose irradiation before surgery of extra hepatic bile duct carcinoma. No other reports about the use of preoperative radiotherapy for bile duct tumors have been published.
The role of additional radiation therapy after resection in patients with hilar cholangiocarcinoma is controversial. In a previous study from our institution, resection with postoperative radiotherapy showed a significantly improved survival as compared to resection only. Other retrospective studies have also suggested that radiation therapy augments survival in patients with hilar cholangiocarcinoma, especially in the palliative setting. In a prospective study, Pitt et al. suggested that postoperative radiation for perihilar cholangiocarcinoma has no effect on either length of survival or quality of life. Application of radiotherapy for bile duct carcinoma may even result in substantial morbidity. Virtually no data have been reported on complications of adjuvant radiation after resection for hilar cholangiocarcinoma, especially not in regard with the use of intraluminal brachytherapy.

Palliative treatment

The main purpose of palliation in irresectable hilar cholangiocarcinoma is relief of symptoms as jaundice and cholangitis. There is however no consensus if percutaneous or endoscopical biliary palliative drainage is preferable above a surgical bypass procedure. Also the role of radiotherapy in treatment of these irresectable hilar cholangiocarcinoma remains controversial. Throughout the years, extensive experience with endoscopical biliary drainage for irresectable tumors has accumulated in our institution, and this procedure is always the first choice in palliation of hilar cholangiocarcinoma. Even in patients who underwent explorative laparotomy, endoscopical palliation was generally preferred above a biliary-enteric bypass procedure in case of irresectability. However, as previously reported, endoscopic biliary drainage in extended hilar cholangiocarcinoma is technically more difficult and is accompanied by more complications. Therefore the question remains, when the tumor is not resectable during exploration, a surgical bypass procedure should be prefered to achieve good palliation with long-term adequate biliary drainage.
Conclusions
In conclusion, all different diagnostic radiological procedures in the preoperative assessment of hilar cholangiocarcinoma have their limitations. It is difficult to differentiate between benign and malignant lesions, which results in misdiagnosis and mismanagement in patients with these lesions. Furthermore, performing a cholangiogram carries a potential risk of inducing an infection in the obstructed biliary tract, for which drainage is necessary, with the subsequent risk of tumor spill during perturbation of the tumor. When resection is planned, the extension of the tumor will dictate the extension of the resection. At the same time, the high incidence of complications, especially after liver resections, has to be weighed against the low rate of complete tumor clearance and the impact on long-term survival. In addition, the precise role of radiotherapy, in both resectional and palliative treatment has to be analyzed in detail. Finally, when eventually only palliation can be offered in patients undergoing exploration, the question remains if patients should undergo a bilio-digestive bypass procedure.
Aim of the Thesis

Surgical treatment in hilar cholangiocarcinoma is not limited to only performing the resection. Assessment of the tumor and subsequent evaluation of resectability needs a multi-disciplinary approach in which the surgeon plays an important role. In choosing for additional therapy, but also during follow-up, and during further palliative treatment when the tumor is irresectable, the surgeon will guide the patient. All diagnostic and treatment modalities are associated with limitations and complications and should be analyzed carefully to achieve optimal management in these rare tumors.

The studies in this thesis address the problems concerning diagnostic assessment of hilar cholangiocarcinoma and the differentiation of malignant and benign lesions, in which Granular Cell Tumors will be discussed separately. Furthermore, surgical treatment and subsequent complications are analyzed and the role of local resections will be highlighted. The use of radiotherapy, in the preoperative, postoperative and palliative setting is also assessed. Special attention is hereby given to the occurrence of implantation metastases, the complications of intraluminal brachytherapy and the resulting survival benefit. Finally, long-term survival and results of endoscopic palliation are investigated.

Between 1983 and 1998, resection of hilar cholangiocarcinoma has been performed in 112 patients at the Academic Medical Center, Amsterdam, The Netherlands. The operations varied from local resections to extended liver resections, including vascular resections and reconstructions, and were performed by different surgical teams. Not only surgical treatment but also preoperative assessment changed during the years. Eventually, all resections had substantial morbidity and mortality, which however was different during the years and clearly influenced the overall benefit of the procedure. In Chapter 2, we retrospectively analyzed all consecutive patients who had undergone resection during this period, with the aim of identifying risk factors for morbidity and mortality. Special attention was paid to preoperative work-up and also to the influence of
different treatment policies resulting from changes in the surgical teams, was a point of consideration during this analysis.

Reports about benign lesions at the hepatic hilum are scarce. Wetter et al. found among 98 consecutive patients, diagnosed as having a cholangiocarcinoma, 8% benign lesions. Also in a previous study from our institution, during the period 1984 to 1990, a 13% false-positive preoperative diagnosis of malignancy in patients resected for a suspicious hilar obstruction, was reported. Because of the considerable incidence of these benign lesions, we have to be aware of inappropriate (surgical) treatment of benign lesions at the hepatic hilum, without a histological diagnosis. The aim of the study described in Chapter 3, was to determine if preoperative diagnosis and staging of hilar cholangiocarcinoma after 1990, resulted in a decrease of false-positive diagnoses of malignancy. Among all consecutive patients who underwent resection of a hilar stricture that was suspicious of a cholangiocarcinoma, we analyzed all patients who eventually were found to have a benign lesion during histopathological assessment. In trying to define suspicious features of a hilar stricture, which could be helpful in future diagnostic work-up, details from clinical presentation and radiological examinations were blindly re-assessed by a panel of specialists, all experienced in hepatopancreatobiliary disorders. Finally, complications and follow-up in this particular group of patients who had undergone a resection for a benign lesion were analyzed.

Within the group of patients with benign lesions at the hepatic duct confluence, 2 patients had granular cell tumors and are described in detail in Chapter 4. These rare tumors are non-metastasizing and have a predilection in the dermal and subcutaneous tissues, especially within the oral cavity, chest wall and extremities. A review of literature is presented, in which a total of 53 cases of biliary granular cell tumors are reported. Like in any malignancy of the gastrointestinal tract, treatment of biliopancreatic tumors requires local and regional control of the disease and therefore, radical surgical excision of the tumor has classically been the mainstay of therapy. As mentioned before, patients
with Bismuth type I and II Klatskin tumors are generally treated by local resection. Type IIIa/b tumors are treated with hilar resection in combination with a hepatic lobectomy. However, during a specific period in the past (1988-1992), type III tumors were preferably treated with local resection in an attempt to obtain good palliation with adequate biliary drainage. In view of the discussion regarding local resection vs. radical resection, the study presented in Chapter 5 was undertaken to assess the effectiveness of local resection in the management of proximal bile duct tumors, mid-choledochal duct tumors and ampullary tumors. Although these tumors each have their specific, diagnostic and management problems, experience with local resections for these tumors at different locations along the extrahepatic biliary tract has accumulated in our institution and results after local resections are evaluated.

In a previous study, a high incidence (95%) of cytologically proven tumor cells was found in bile of patients with a proximal bile duct carcinoma after endoscopic biliary drainage. A potential hazard of bile spill is the occurrence of implantation metastases in the operative field. The purpose of the study described in Chapter 6 was to analyze the development of implantation metastasis in drain tract scars and laparotomy scars in patients who had undergone resection of a Klatskin tumor following preoperative endoscopic biliary drainage.

To prevent implantation metastases, preoperative radiotherapy was introduced in our institution in 1990, and in patients with resectable hilar bile duct carcinoma who had undergone preoperative stent placement during ERCP, 10.5 Gy was administered in 3 fractions during three consecutive days preceding surgery. In all patients, surgery was performed within one week after the last fraction. In Chapter 7, the results of this preoperative irradiation were evaluated with respect to reduction of implantation metastases after resection of hilar bile duct carcinoma. Also special attention was given to the potential adverse effects of this specific treatment and to the influence on survival.
The role of adjuvant radiation therapy after resection in patients with hilar cholangiocarcinoma remains an issue. The benefit regarding survival has to be weighed against the substantial morbidity of radiation therapy. During the past 15 years, in which postoperative radiotherapy was given after resection for hilar cholangiocarcinoma in our institution, only external irradiation was given with a mean of 46 Gy or radiotherapy was given by a combination of external (mean 42 Gy) and intraluminal brachytherapy (10 Gy), using iridium-192 wires. These wires were used to load catheters, which were placed across the bilio-digestive anastomoses, via the distal end of the Roux-en-Y loop that was brought out for this purpose as a terminal jejunostomy at the time of resection. The aim of the study described in Chapter 8, was to assess the results and complications of additional radiotherapy after resection of hilar cholangiocarcinoma, with special interest in the difference of using external radiation alone or in combination with intraluminal brachytherapy.

In Chapter 9, the long-term survival of patients that had undergone resection of a Klatskin tumor was assessed, in an attempt to determine prognostic factors for survival. Between 1983 and 1991, 79 consecutive patients with a carcinoma of the hepatic duct confluence underwent resection in our institution. Patients were included until 1991, to obtain a minimum of 5 years follow-up. Hospital mortality was 15/79 (19%). All remaining patients were studied in detail.

Various histopathological characteristics of the tumor were assessed, including lymph node involvement, multifocality of the lesion, and residual tumor in the surgical margins. The tumors were graded on both the histologic and cytologic level according to two main categories of differentiation. Tumor DNA content of the specimens (diploid or aneuploid tumor status), as determined by flow cytometric cell analysis, was also included in this analysis. Besides these histopathological characteristics, tumor extension found during preoperative diagnosis and results of adjuvant therapy were also assessed and a comparison of all characteristics was made between long-term survivors and the other patients.
Patients referred to our surgical unit, who were fit to undergo an explorative laparotomy, should be considered to comprise a selected group, compared to the patients who, because of apparent irresectability during radiological assessment, primarily underwent endoscopic palliation. Furthermore, as previously reported, endoscopic palliation in especially Bismuth type III and IV hilar cholangiocarcinoma is technically difficult and accompanied by more complications when compared to the other types. Therefore in Chapter 10, patients with a Bismuth type III or IV tumor were analyzed, who were referred for resection but eventually were considered irresectable. Results regarding direct and long-term complications as well as survival were compared with results from literature, with special attention to bilary-enteric bypass procedures. A comparison was made between patients who underwent an explorative laparotomy and patients who did not. Finally, also the role of radiotherapy in palliation of these tumors was analyzed.

In Chapter 11, the results of the studies presented in this thesis have been shortly summarized and discussed with respect to clinical implications and future studies.
Reference List


