Surgical strategies in the management of hilar cholangiocarcinoma
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CHAPTER

11

Summary and conclusions
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Primary cholangiocarcinoma continue to pose challenging diagnostic and therapeutic problems. From 1983 till 1998, 112 patients with these so called Klatskin's tumors, underwent resection in the Academic Medical Center, Amsterdam, The Netherlands. This thesis deals with the limitations, complications and alternatives of surgical treatment in hilar cholangiocarcinoma. The difficult differentiation from benign lesions, the type of resection and subsequent complications as well as the use of additional radiotherapy and long-term survival are evaluated. Finally, palliative treatment in extended tumors is analyzed.

Because hilar cholangiocarcinoma have not only close relationship to important structures such as the hepatic artery and portal vein, but often shows progression along the proximal biliary tree with perineural and lymphatic involvement, a margin-negative resection is technically demanding and often impossible to achieve. Local resection of these tumors, and especially the combination with partial liver resection, results in substantial morbidity and mortality. Results after resection are analyzed in Chapter 2, describing a period between 1983 and 1998. In this period, 80 consecutive patients underwent a local resection and 32 patients local resection combined with a hemihepatectomy. For evaluation of different treatment strategies during the study, the period was divided in three, 5-years intervals. Postoperative complications occurred in 65% of all patients. The overall hospital mortality was 15% for local resections and 25% for hemi-hepatectomies. There was a significantly lower morbidity and no mortality after local resection during the last 5-years. A higher Bismuth classification showed significant correlation with postoperative morbidity. Extended liver resections and vascular resections and a preoperative albumin level below 35 g/L were found to be significant predictors of increased mortality in univariate analysis. However, more (extended) liver resections resulted in an increased rate of microscopical tumor-free resections. Improved preoperative work-up will result in less unnecessary palliative resections and furthermore, in a selection of patients who can be treated sufficiently with a local resection.
resulting in less complications and in a selection of patients who might benefit from extensive resections.

In an earlier study during the period 1984 till 1990, we reported a 13% false-positive preoperative diagnosis of malignancy in patients resected for a suspicious hilar obstruction. As a consequence, these patients were exposed to substantial complications after these (extended) resections, which might have been avoided. In order to define (non-) suspicious features of a hilar stricture, which could result in future reduction of false-positive diagnosis of cholangiocarcinoma, the aim of the study in Chapter 3 was to re-evaluate all clinical and radiographical characteristics in patients who underwent resection and had eventually a histopathologically proven benign tumor. Among 132 consecutive patients with a tumor mass at the hepatic hilum, resected between 1983 and 1998, 20 patients (15%) had a benign tumor. In this group, postoperative morbidity was 68% and mortality was 5%. Three patients died during follow-up, however, not due to primarily disease-related complications and only 33% of the patients had no symptoms. A panel of specialists, all experienced in hepato-pancreatobiliary disorders, blindly re-assessed all medical files and radiological examinations of these patients. The combination of symptoms was considered not suspicious in 3/19 (16%) patients. At US, only 1/16 (6%) patients had no suspicious features. In 4/18 (22%) patients the cholangiography images were considered not suspicious. The overall index of suspicion however, primarily based on the investigations giving the highest suspicion, was positive in 50% of the patients and highly positive in the other 50%. Therefore, careful review of all preoperative information confirmed the initial diagnosis. Only the grade of suspicion differed but would have had no influence on the choice of treatment. Due to limitations of current diagnostic tools, a false-positive preoperative diagnosis of malignancy cannot be excluded, resulting in a 15% resection rate of benign lesions in this series of suspicious hilar strictures.

Among these patients with a benign lesion, 2 patients had a granular cell tumor. In Chapter 4, these 2 patients are described and a review of the literature regarding these lesions is given. 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, but may present at any location. In literature, so far, 53 cases of biliary granular cell tumors have been reported. These tumors often present in young black women with initial symptoms of abdominal pain, jaundice or both. At preoperative examination, hilar granular cell tumors are difficult to differentiate from cholangiocarcinoma, sclerosing cholangitis or more common benign biliary tumors. Therefore, most of these cases were not diagnosed until surgery. Excision with tumor free margins is the only appropriate treatment and is associated with good prognosis.

Besides hilar cholangiocarcinoma, also mid-choledochal duct tumors and tumors arising from the papilla of Vater are potentially amenable to local resection. Chapter 5 reviews the experience in the AMC, with local resection of these conditions. From 1983-1998, local resection was undertaken in 80 patients with hilar cholangiocarcinoma (52 patients with type I and II tumors, and 28 patients with type III tumors). Negative surgical margins were achieved after local resection in 10 patients with type I and II tumors (19.2%), and in one patient with a type III tumor (3.6%). Among 32 patients who underwent a hilar resection combined with liver resection, 5 patients had negative surgical margins (15.6%). From 1993-1998, 13 patients underwent resection of a mid-choledochal duct carcinoma. In 8 patients, a local resection was performed, and in 5 patients, a subtotal pancreateoduodenectomy (PPPD). Five patients had negative surgical margins, 2 after local resection (25%) and 3 after PPPD (60%). From 1993-1997, 9 patients underwent local resection of a presumed ampullary adenoma that proved a carcinoma. In 4 patients with T1 tumors, resection of the carcinoma was locally complete (44%). Additional PPPD was performed in 6 patients, including the 4 patients with complete local resections, showing no residual tumor at the previous site of excision, but lymphnode metastases in two resection specimens. In conclusion, local resection is applicable to Klatskin type I and II tumors. Local resection may be considered in the proximally located, mid-choledochal duct carcinomas but, when located closer to the pancreas, PPPD is the preferred treatment. For ampullary adenomas, local resection is feasible unless frozen section examination raises suspicion on a malignancy. Local
resection of even limited ampullary carcinomas is not advisable because of lymphatic dissemination of the tumor and consequently, inadequate clearance.

We found a high amount of patients with implantation metastases during follow-up of patients after resection of a hilar cholangiocarcinoma. A remarkable fact was that all these patients had undergone preoperative ERCP with stent placement. Therefore, in Chapter 6, possible risk factors leading to implantation metastases were analyzed. Fifty-two patients who had undergone a resection of a Klatskin tumor were divided into two groups, comparing patients who had had preoperative ERCP and stent placement (n=41) and patients without preoperative drainage (n=11). Eight patients developed implantation metastases within 1 year after resection, all of whom had preoperative stent placement (20%). None of the patients without preoperative stenting developed implantation metastases. This study shows that preoperative ERCP with biliary drainage is associated with a higher frequency of implantation metastases after resection of Klatskin tumors. A properly planned prospective study, however, is needed to determine whether bile duct stenting in patients with resectable bile duct tumors, is a true risk factor for the development of implantation metastases.

Starting in 1990, preoperative radiotherapy was introduced in our institution, in patients with resectable hilar cholangiocarcinoma, who had undergone preoperative stent placement during ERCP, in an attempt to prevent the occurrence of implantation metastases. The aim of the analysis presented in Chapter 7, was to evaluate the results of preoperative irradiation with regard to a possible reduction of implantation metastases. Twenty-one patients with a proximal bile duct tumor who had undergone resection following preoperative irradiation were retrospectively analyzed. Preoperative radiation therapy consisted of three fractions of 3.5 Gy external beam irradiation of the hilar area. Preoperative biliary drainage was performed in 19 patients (90%) and all patients received preoperative radiotherapy. No complications were noted during preoperative radiotherapy. Preoperative radiotherapy did not seem to improve survival time but eventually, none of the patients developed implantation metastases, within a follow-up time of 2 to 79 months. The results of this study suggest that preoperative
radiotherapy decreases the risk of implantation metastases in patients who have undergone preoperative drainage. However, to be certain about the role of preoperative radiotherapy, a randomized study is required.

The need for postoperative radiation therapy after resection of hilar cholangiocarcinoma is questionable. A recent prospective study suggests that postoperative radiation has no effect on either the length of survival or quality of life. The aim of the study presented in Chapter 8, was to assess the value of radiotherapy, and especially intraluminal brachytherapy, after resection of hilar cholangiocarcinoma, by analyzing long-term complications and survival. Between 1983 and 1998, 91 patients survived the postoperative period after resection of a hilar cholangiocarcinoma. Twenty patients had no additional radiotherapy, 30 patients had only external radiotherapy (46 ± 11 Gy) and 41 patients had a combination of external (42 ± 5 Gy) and intraluminal brachytherapy (10 ± 2 Gy) via a jejunostomy at the distal end of the Roux-en-Y loop used for the biliary-enteric anastomoses. Overall, 88% of the patients had late complications, with a significantly higher rate in patients receiving external beam irradiation and brachytherapy. Second to abdominal pain (56%), cholangitis (49%) was the most frequent complication and occurred significantly more often in patients who had had brachytherapy. Ileus (36%) was the third most common late complication associated with additional radiotherapy. Retrograde bile leakage after closure of the temporary jejunostomy was a troublesome complication in 24% of patients treated with brachytherapy. Overall median survival after treatment with adjuvant radiotherapy was higher than after resection without additional radiation (24 months vs. 8 months, respectively). There was, however, no significant benefit of the use of intraluminal brachytherapy. Long-term complications associated with adjuvant radiotherapy were substantial and were even increased in patients who had brachytherapy. Therefore, in our institution, additional radiotherapy after resection of hilar cholangiocarcinoma is continued by giving external beam irradiation only.

In an attempt to determine prognostic factors for long-term survival, in Chapter 9, all patients who underwent a resection for a hilar cholangiocarcinoma, were analyzed
retrospectively. To obtain a minimum of 5 years follow-up, patients were included until 1991. Fifteen patients died due to postoperative complications and were excluded from this survival analysis. Among the remaining 64 consecutive patients, 12 patients (19%) had a long-term survival of more than 5 years. In relation with preoperative Bismuth classification, there were 3/15 (20%) long-term survivors with type I tumors and 9/26 (35%) long-term survivors with type II tumors. In the group of type III and IV tumors, there were no long-term survivors. Concerning type of resection, 9/51 (18%) patients had long-term survival after local resection and 3/13 (23%) patients after local resection combined with hemihepatectomy. Complete tumor free surgical specimen margins were found in only 4/64 cases (6%), of which only one survived for more than 5 years. Of the 12 long-term survivors, five died after 5 years, of which 2 had developed metastases and one a local recurrence. The mean survival was 34 months, with a median survival of 19 months. Eventually, besides preoperative Bismuth classification of the tumor, also absence of multifocality, diploid type tumors and negative proximal bile duct margins at histopathological examination, were found to be significant prognostic factors for long-term survival.

Due to extensive experience with ERCP in our institution, palliative treatment of hilar cholangiocarcinoma is predominantly achieved by means of endoscopic biliary drainage. Survival after palliative stenting is however short, and probably due to patient selection, better results are reported after bilio-digestive bypass procedures. Furthermore, endoscopic palliation in type III and IV hilar cholangiocarcinoma is less satisfactory in respect with success and complication rate. In Chapter 10, patients with type III and IV tumors were analyzed retrospectively, with the aim to compare results after endoscopic palliation in a concise group of patients, who were primarily referred for resection. Between 1992 and 1999, 41 patients were considered irresectable during additional diagnostic work-up in our department, including an explorative laparotomy in 16 patients. In all patients, biliary drainage was established by means of ERCP with insertion of endoprostheses. In 12 patients, additional PTBD was performed. Overall median survival was 9 months, which is relatively long. During follow-up, biliary
drainage remained the leading problem. In 91% of patients, replacements of endoprosthesis were needed, with a mean of 4 ± 3.5 times. Adjuvant radiation had no influence on survival. Because, in the literature, biliary-enteric bypass procedures showed effective relief of symptoms and accordingly, excellent palliation, we have come to the conclusion, when already a surgical exploration is performed in patients with type III and IV tumors, a surgical bypass procedure should be performed.

**General discussion and future perspectives**

Hilar cholangiocarcinoma are difficult to treat and need a multidisciplinary approach in specialized referral centers. Due to limitations of imaging techniques and based on the intention of not missing a potentially curable cancer, resection of a benign lesion mimicking a malignant lesion cannot be avoided in 15% of patients with suspected hilar cholangiocarcinoma. Resection can generally be performed by local resection for Bismuth type I and II tumors. For type III tumors, however, an additional hemi-hepatectomy is mandatory. In our opinion, type IV tumors carry a high risk of leaving behind tumor tissue, and therefore extended resections in these tumors are better avoided.

Overall, hospital morbidity (65%) and hospital mortality (14%) after these resections remain high, especially after vascular and extended liver resections. In most recent years however, a different preoperative assessment was adopted in which laparoscopy with ultrasound was the major difference. A better preoperative diagnosis led to a better operative plan and unnecessary (extended) palliative resections could be avoided in 40% of patients. This, in combination with better results after local resection, resulted in lower overall complication rates. During the last 5 years, even an overall higher margin negative resection rate (32%) was achieved. It remains to be seen however, if in the future this also will lead to higher survival rates.

Overall median survival in patients with hilar cholangiocarcinoma after resection was 21 months. There was however a significant difference between the use of adjuvant radiotherapy (24 and 8 months, with and without irradiation, respectively). Possibly, the
survival advantage of additional radiotherapy relates to the high proportion of tumor margin positive resections (86%). Among the long-term survivors (>5 years, 19%), preoperative Bismuth classification, absence of multifocality, diploid type tumors and negative proximal bile duct margins at histopathological examination, were found to be the only significant prognostic factors for survival.

Long-term complications associated with adjuvant radiotherapy were substantial, however difficult to distinguish from symptoms of defective drainage or tumor recurrence. The combination of external beam irradiation with brachytherapy by means of a temporary jejunostomy did not show any benefit on either the length or the quality of survival, but generated more complications and therefore, has been abandoned. Recently, we suggest additional radiotherapy (50 Gy) in all patients who have undergone a resection for a hilar cholangiocarcinoma, delivered exclusively by external beam irradiation. And, because of the risk of development of implantation metastases (20%), which was associated with patients who had undergone biliary drainage before resection, we also advise preoperative radiotherapy of 10.5 Gy in these patients. Results after preoperative radiotherapy suggest that the risk of implantation metastases decreases, without any specific adverse effects.

The choice of palliative treatment in hilar cholangiocarcinoma remains controversial. The type of palliation seems to depend on local expertise in a center. However, when patients are primarily referred for resection and eventually tumor excision appears not possible, this selected group of patients will probably survive a considerable time (median survival: 9 months) and more complications will be anticipated during follow up. And, because we know that in advanced hilar cholangiocarcinoma endoscopic palliation is less satisfactory with respect to success and complication rate, the possible adverse effects of surgical palliation have to be weighed against the complications associated with endoscopic treatment. Therefore, in unresectable disease determined at explorative laparotomy, a surgical bypass procedure is probably the preferable option. Furthermore, for palliation, radiotherapy did not prolong survival and therefore was abandoned.
Concerning future perspectives, diagnostic laparoscopy with US, thin-section multiphasic spiral CT scan and MRCP are promising and need further clinical assessment. MRCP has potential to replace ERCP, avoiding the adverse effects of the latter, including alteration of bacterial flora in the bile ducts and detachment of tumor cells. Also the use of other diagnostic tools, such as serum tumor markers and endoscopic US-guided fine-needle aspiration, need to be further explored. Several, limited studies have even documented the ability of positron-emission-tomography (PET) to detect cholangiocarcinomas as small as 1 cm in diameter.

Regarding treatment, further development of chemotherapy, in which combinations of different agents are tested, can possibly offer prolonged survival. Preoperative strategies, however, such as chemo-radiotherapy are not realistic in view of the high rate of misdiagnosed, benign lesions in the hepatic hilum. Furthermore, it is questionable if major improvement in survival will result from more aggressive and advanced surgical techniques or radiation therapy. Instead, perhaps early detection or genetic alteration of the tumor will bring more hope for the future.