Surgical strategies in the management of hilar cholangiocarcinoma
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The occurrence of implantation metastases after resection of Klatskin tumors

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Summary

Background: We found a high proportion of patients with implantation metastases during follow-up after resection of a proximal cholangiocarcinoma. A remarkable fact was that all these patients had undergone preoperative ERCP with placement of a stent. ERCP is frequently used in the assessment of the proximal extension of Klatskin tumors and is usually followed by stent insertion for biliary drainage. The aim of this study was to analyze in this series of patients, possible risk factors leading to implantation metastases.

Method: Fifty-two patients who had undergone 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).

Results: Eight patients developed implantation metastases within 1 year after resection, all of whom had undergone preoperative stent placement (8/41 (20%)). None of the patients without preoperative stenting developed implantation metastases. In 22 patients bile samples were taken during operation. Sixteen (72.7%) patients had malignant cells and 4 (18.2%) patients atypical cells in the bile sample. There was no difference in cytology results between the two groups.

Conclusion: This study suggests 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.
Introduction

Cholangiocarcinoma of the hepatic duct confluence (Klatskin tumor) is an uncommon malignancy associated with poor prognosis and a high mortality rate. Proximal extension of the tumor determines resectability of the lesion and, therefore, reliable assessment of the intra-and extrahepatic bile ducts is crucial to planning a patient for resection or palliative treatment. Endoscopic retrograde cholangiopancreatography (ERCP) is a diagnostic procedure applied in most of the jaundiced patients that are presented at our institution. Cholangiographic images can provide valuable information concerning the proximal extent of the tumor and can help to define the type of hilar obstruction in accordance with the Bismuth classification. At the same time, the biliary tract is usually drained by passing one or more stents into the bile ducts across the obstruction. The use of stents in patients with a tumor in the hepatic duct confluence, however, also brings along adverse effects caused by manipulating obstructed bile ducts. Micro-organisms are introduced into the bile ducts giving rise to cholangitis, and perturbation of the tumor by the stent may cause tumor cells to detach, contaminating the bile with malignant cells. In previous studies, high incidences of cytologically proven tumor cells were reported, in bile of patients with a proximal bile duct carcinoma after endoscopic biliary drainage.

Bile spill will take place in all patients during surgery in the process of resection before the biliary anastomoses have been constructed. A potential hazard of bile spill is the occurrence of implantation metastases in the operative field. We found a high proportion of patients with implantation metastases during follow-up after resection of a proximal cholangiocarcinoma. A remarkable fact was that all these patients had undergone preoperative ERCP with placement of a stent. The aim of this study was to analyze risk factors for 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.
Material and Methods

At our institution, resections for proximal cholangiocarcinoma have been carried out since 1983. After 1990, patients were enrolled in a protocol of preoperative radiotherapy, and therefore were excluded from the present analysis. All patients with (peritoneal) metastases at the time of exploration did not undergo resection and therefore, were not assessed in this analysis. In this period, 66 patients underwent resection of a Klatskin tumor. Fourteen patients died postoperatively (hospital mortality rate 21.2%) and were excluded from this analysis. The occurrence of implantation metastases was assessed in the remaining 52 patients. There were 32 (61.5%) men and 20 (38.5%) women, with median age 57.5 (range 18-74 years) years.

After diagnostic ERCP, one or two stents were inserted into the bile ducts as a standard procedure to relieve jaundice, unless drain insertion was not possible. Plasma bilirubin levels were assessed shortly before surgery to evaluate the effect of biliary drainage after ERCP and stent placement.

Local resection was carried out for type I and II tumors according to the Bismuth classification. This procedure consisted of excision of the extrahepatic bile duct, its confluence and part of liver segment IV and/or segment I, when indicated. For patients with tumor extension in accordance with Bismuth classification type III, hilar resection was usually combined with partial liver resection.

Postoperative radiotherapy was given either as external beam irradiation or as a combination of external beam irradiation and internal irradiation applied intraluminally at the hepatic duct anastomoses. Access to the biliary tract was provided by extending the Roux- and Y loop to the abdominal wall, creating a temporary jejunostomy. The overall irradiation dose was 55 Gy in all patients.

The diagnosis of cholangiocarcinoma was confirmed histopathologically in all resected specimens. Resection as well as dissection margins were examined and assessed for microscopical radicality. Bile samples were examined for malignant cells in 22 patients.
Follow-up of patients occurred until death or until evaluation for this study. All implantation metastases were histologically proven after biopsy.

Statistical analysis
The chi-square test (Pearson; Mantel-Haenszel and two tails Fischer's exact test, table 1) was used in SPSS®️, to assess the significance of differences between groups. Only probabilities of < 0.05 were accepted as significant.
**Results**

Forty-one patients had undergone endoscopic biliary drainage with stent placement (4 in combination with percutaneous transhepatic drainage) prior to operation (group I) whereas 11 (21.2%) patients (group II) were not drained preoperatively. Technical problems such as inability to pass the tumor or the absence of congestion of bile proximal to the tumor, were the main reasons for not succeeding in placing an endoprosthesis.

Doppler ultrasonography (n=40) and percutaneous transhepatic cholangiography (n=7) was helpful to determine the proximal extent of the tumor. There was no significant difference between the two groups in regard with Bismuth classification, type of resection, number of hepatico-jejunostomies or average total operation time. The characteristics of both groups of patients are shown in table 1.

Eight patients (15.4%; 2 women and 6 men, median age 60, range 52-72 years) presented with an implantation metastasis in drain tract scar or laparotomy scar within one year after the initial operation. All implantation metastases were found among patients of group I (19.5%). In group II, in which patients had no preoperative biliary drainage at all, no implantation metastases were encountered during follow-up (table 1). Four out of 8 patients (50%) with implantation metastases had no postoperative radiotherapy, whereas 3 patients (37.5%) received a combination of internal and external radiotherapy, and 1 (12.5%) only external radiotherapy.

The bile of 22 patients was examined cytologically for malignant cells, including 6 of the 8 patients with implantation metastases. In the latter 6 patients, 4 bile samples (66.7%) revealed tumor cells and in 1 sample (16.7%) atypical cells were found. Of 16 patients with no signs of implantation metastases, 12 patients (75%) had malignant cells and 3 patients (18.75%) atypical cells in the bile. In summary, of all 22 patients who had cytological assessment of the bile, 16 patients (72.7%) had malignant cells and 4 patients (18.2%) atypical cells in the bile. Comparing the two groups, with or without preoperative biliary stent placement, no significant (p = 0.60) difference in the percentages of malignant and atypical cells in the bile samples was found (table 2).
### TABLE 1. CHARACTERISTICS OF PATIENTS WHO HAD UNDERGONE PREOPERATIVE BILIARY DRAINAGE (GROUP I) OR WHO HAD NO PREOPERATIVE DRAINAGE (GROUP II)

<table>
<thead>
<tr>
<th></th>
<th>Group I (n=41)</th>
<th>Group II (n=11)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>27M/14F</td>
<td>5M/6F</td>
<td>0.29</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>58 (range 21-74)</td>
<td>52 (range 18-70)</td>
<td></td>
</tr>
<tr>
<td>Bismuth classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Type I</td>
<td>24% (n=10)</td>
<td>9% (n=1)</td>
<td></td>
</tr>
<tr>
<td>-Type II</td>
<td>37% (n=15)</td>
<td>64% (n=7)</td>
<td></td>
</tr>
<tr>
<td>-Type III</td>
<td>24% (n=10)</td>
<td>27% (n=3)</td>
<td>0.49</td>
</tr>
<tr>
<td>-Type IV</td>
<td>2.5% (n=1)</td>
<td>0% (n=0)</td>
<td></td>
</tr>
<tr>
<td>Missing observations**</td>
<td>12.5% (n=5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local resection</td>
<td>78% (n=32)</td>
<td>73% (n=8)</td>
<td>0.70</td>
</tr>
<tr>
<td>-with partial liver resection</td>
<td>22% (n=9)</td>
<td>27% (n=3)</td>
<td></td>
</tr>
<tr>
<td>Radicability of resection</td>
<td>2% (n=1)</td>
<td>18% (n=2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Total bilirubine blood level***</td>
<td>117 μmol/l (12-511)</td>
<td>235 μmol/l (14-412)</td>
<td>0.008</td>
</tr>
<tr>
<td>External radiotherapy</td>
<td>14% (n=6)</td>
<td>18% (n=2)</td>
<td></td>
</tr>
<tr>
<td>Combined radiotherapy</td>
<td>49% (n=20)</td>
<td>55% (n=6)</td>
<td>0.84</td>
</tr>
<tr>
<td>No radiotherapy</td>
<td>37% (n=15)</td>
<td>27% (n=3)</td>
<td></td>
</tr>
<tr>
<td>Implantation metastases</td>
<td>20% (n=8)</td>
<td>0%</td>
<td>0.18</td>
</tr>
</tbody>
</table>

* Preoperative Bismuth classification
** In 5 patients the definitive classification was not retrieved
*** Measurements in the week before operation. For group I after stent placement
# See statistical analysis: ¹Pearson test; ²Mantel-Haenzel test; Two-tailed Fischer's exact test

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**CHAPTER 6 THE OCCURRENCE OF IMPLANTATION METASTASES AFTER RESECTION OF KLATSCHIN TUMORS**
Of all 52 patients only 3 (5.8%) patients had microscopically free resection margins (free resection as well as dissection margins). Only one of these 3 patients had preoperative drainage (table 1). Remarkably, this patient developed an implantation metastasis. None of the other two patients with radical resected tumors, developed implantation metastases.

The overall median survival of the 8 patients with implantation metastases was 9.4 months. The overall median survival of the 44 patients without implantation metastases was significantly better (Mantel-Haenzel ratio of 0.043), with a median survival of 21.5 months. Three patients are still alive. None of them has developed an implantation metastasis (fig.1).

<table>
<thead>
<tr>
<th>Cytology Results</th>
<th>Group I (n=17)</th>
<th>Implantation metastases</th>
<th>Group II (n=5)</th>
<th>Implantation metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant Cells</td>
<td>13 (76.5%)</td>
<td>4 (31%)</td>
<td>3 (60%)</td>
<td>0</td>
</tr>
<tr>
<td>Atypical Cells</td>
<td>3 (17.6%)</td>
<td>1 (33%)</td>
<td>1 (20%)</td>
<td>0</td>
</tr>
<tr>
<td>Benign Cells</td>
<td>1 (5.9%)</td>
<td>1 (100%)</td>
<td>1 (20%)</td>
<td>0</td>
</tr>
</tbody>
</table>
FIGURE 1. KAPLAN MEIER SURVIVAL CURVE IN RELATION WITH THE EXISTENCE OF IMPLANTATION METASTASES

- PATIENTS WITHOUT IMPLANTATION METASTASES
- PATIENTS WITH IMPLANTATION METASTASES
- PATIENTS STILL ALIVE

SURVIVAL IN MONTHS
Discussion

It is well known that bile duct epithelium is continuously shed into the bile. Likewise, in case of an epithelial proliferation as in carcinoma of the hepatic duct confluence, tumor cells exfoliate and contaminate the bile. The insertion of stents through the tumor obviously enhances this process by disengaging tumor cells at the site of obstruction. In this study, unfortunately, the number of analyzed bile samples were too low (41.1% and 45.5%, in both groups, respectively), to draw firm conclusions.

However, despite the fact that the occurrence of benign cells in the group without preoperative stent placement was threefold higher than in the group with stent placement, the incidence of malignant cells in bile samples of both groups, was not significantly different. Probably, there is another, unknown factor during stent placement, besides the presence of malignant cells, which contributes to the development of implantation metastases.

Spill of bile containing tumor cells, during surgery of the bile ducts, is a potential hazard for the occurrence of implantation metastases. Especially when many small bile ducts are involved, there is a continuous spill of bile while performing the biliary anastomoses. The occurrence of implantation metastases not only depends on possible spill of tumor cells, but is also promoted by a favorable environment for seeding of tumor cells. Experimental data suggest that an extensive healing wound enhances the growth of metastatic tumors. Implantation metastases encountered in this study were accordingly found in the scars of laparotomy wound or drain tract.

Percutaneous transhepatic cholangiography with drainage and ERCP are widely used for the diagnosis and treatment of malignant biliary obstruction. In our institution, the majority of patients with a suspected proximal cholangiocarcinoma have undergone ERCP with stenting, before referral to our surgical department. Several studies in the past, however, have shown that preoperative drainage probably has no beneficial effects in the preoperative management of hilar cholangiocarcinoma. Major complications have been associated with these interventional procedures. The main complications reported are
cholangitis (14-37%), hemorrhage, bile leakage and seeding of malignant cells.\textsuperscript{12,14,26} It is still doubtful whether these preoperative procedures have to be performed routinely.

Despite the frequent use of percutaneous transhepatic cholangiography with drainage in the diagnosis and treatment of malignant biliary disease, there are only occasional reports (total of 18 patients found in literature) of associated tumor seeding in catheter track after percutaneous transhepatic drainage.\textsuperscript{12,14,15,17,21-25} ERCP has been regarded as a safer option compared to percutaneous transhepatic cholangiography with drainage.\textsuperscript{14}

However, this study suggests that ERCP and stent insertion for hilar tumors is associated with a higher frequency of implantation metastases, after resection.

Preoperative radiation therapy was shown to be effective in preventing scar implantation metastases in bladder cancer.\textsuperscript{26} In our institution, therefore, preoperative low-dose irradiation is applied as of 1990, in patients with potentially resectable hilar tumors after preoperative biliary drainage. This approach seems hopeful in order to reduce the risk of implantation metastases. A study concerning the results of preoperative radiotherapy is currently underway.

The hospital mortality rate in this series of patients of 21.2% is high compared with modern standards. However, this series of patients was operated before 1990. During the last 5 years in our institution, the hospital mortality rate after local resections and combined liver resections for proximal bile duct tumors was 12%, which is comparable with results from recent studies.\textsuperscript{27}

In conclusion, we assessed the occurrence of implantation metastases in 52 surviving patients after surgery for Klatskin tumor. Implantation metastases were seen within one year in 8 patients, who all had preoperative biliary stent placement. None of the remaining patients in the same period, who had not undergone preoperative biliary stent placement, developed implantation metastases. These observations suggests that preoperative transtumoral stenting of Klatskin tumors is associated with a higher frequency of implantation metastases. A properly planned prospective study is needed to answer the question, whether bile duct stenting in patients with resectable bile duct tumors, is a true risk factor for the development of implantation metastases.
Reference List


CHAPTER 6 THE OCCURRENCE OF IMPLANTATION METASTASES AFTER RESECTION OF KLATSKIN TUMORS