Surgical strategies in the management of hilar cholangiocarcinoma

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CHAPTER 9

Long-term survival after resection of proximal bile duct carcinoma (Klatskin tumors)

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Abstract

This retrospective study in 79 surgically treated patients with a proximal bile duct carcinoma, revealed 12 patients [median age (range): 59.5 years (21-73)] who survived for more than 5 years. These 12 patients were analyzed in order to identify specific patient characteristics for long-term survival. Fifteen patients died due to postoperative complications and were excluded from this survival analysis.

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 hemi-hepatectomy. Complete tumor free surgical specimen margins were found in only 4/64 cases (6%), of which only one survived for more than 5 years. Negative proximal bile duct margins, absence of multifocality and diploid tumors showed a significant correlation with long-term survival. There was no significant correlation between long-term survival and postoperative radiotherapy.

Of the 12 long-term survivors, five died after 5 years, of which 2 had developed metastases and one a local recurrence. The other two died of a metastasis of an ovarian adenocarcinoma and of cachexia, respectively. The mean survival of the 64 patients analyzed in this study (in which hospital mortality was excluded) was 33.7 months, with a median survival of 18.8 months.

In conclusion, preoperative Bismuth classification of the tumor, 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 long-term survival.
Introduction

It is now 31 years since Klatskin first reported on adenocarcinoma of the hepatic duct confluence\(^1\) and still, there are many controversies regarding the management of this lesion. The range of therapeutic modalities varies from a curative approach by performing extensive liver resections - in some cases even total hepatectomy and liver transplantation\(^2\) - to a more palliative approach in which a surgical bypass, or even percutaneous or endoscopic stent insertion is undertaken only, with or without radiotherapy.\(^4\) Several studies have concluded that radical excision of the lesion offers the best treatment option with respect to long-term survival.\(^7\) However, curative resections are difficult to achieve due to the unfavorable location of the tumor, its tendency to grow into the perineural tissue, and its infiltration proximal into the biliary tree and the liver.\(^12\) Some authors argue that due to multifocal presentation of the tumor, the addition of a hepatic resection to hilar excision will not lead to more curative resections.\(^1\) Others, on the other hand, doubt if a nonradical resection will result in adequate biliary drainage and long-term palliation.\(^4\) In view of these controversies, we assessed the outcome of a series of patients that had undergone resection of a Klatskin tumor, in an attempt to determine prognostic factors for long-term survival.
Patients and Methods

Patients
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. There were 28 women and 51 men with a median age of 58 years (range: 18-74 yr.). Fifteen patients died due to postoperative complications (hospital mortality rate 19%). Twelve of these patients died within 30 days postoperatively (30-day mortality rate 15%). Nine patients died after a local resection and 6 after a combination of local resection and (extended) hemi-hepatectomy. They died due to the following complications: peri-operative blood loss (n=9); multiple organ failure (n=7); sepsis (n=3); liver abscesses (n=6), and bile leakage (n=2). Of the remaining 64 patients, we identified 12 patients who survived five years or longer.

Pre-operative work-up
The preoperative diagnosis of a proximal bile duct tumor was based on ultrasonography, endoscopic retrograde cholangio-pancreaticography (ERCP), percutaneous transhepatic cholangiography (PTC), angiography or cytology obtained at ERCP. The tumors were classified according to the system proposed by Bismuth-Corlette.14 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.

Surgical procedures
In our institution, the standard surgical procedure for type I and II tumors is local hilar resection. In case of posterior infiltration into the liver parenchyma, the resection included the caudate lobe. When parenchymal involvement occurred anteriorly, as was
often the case in larger type II tumors, (part of) segment IV was excised. For type III
tumors, hilar resection is carried out in combination with (extended) hemi-hepatectomy.
Type IV tumors are considered unresectable and are palliated endoscopically. In
some patients, the preoperative Bismuth classification was adjusted during surgical
exploration because of apparent, more proximal tumor extension. These patients had a
hemi-hepatectomy in addition to the preoperatively planned local hilar resection. In a
small number of patients, in whom the tumor ultimately was diagnosed as type III or IV,
a macroscopically non-radical local resection was carried out as a palliative biliary
drainage procedure. Occasionally, regional vascular structures were resected. Frozen
section examinations of the proximal and distal resection margins of the bile duct(s)
were obtained during the operative procedures.

Pathology
Of all 64 remaining patients (after exclusion of peri-operative mortality), the histologic
specimens of 63 patients were reviewed (one resection specimen could not be retrieved).
Various histopathological characteristics of the tumor were assessed, including lymph
dnode 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, and were classified as follows: highly to moderately (A), and
moderately to poorly (B). This grading system was chosen because each tumor showed,
except for moderately differentiated regions, also either highly or poorly differentiated
areas; only occasionally was a combination of A and B observed in the same tumor.

Histologic grading: adenocarcinoma was classified as highly differentiated when tumor
cells formed glandular structures. It was classified as poorly differentiated when solid
strands of tumor cells were found. Moderate differentiation was featured by
predominantly a cribriform growth pattern of tumor cells.

Cytologic grading: tumor cells were graded as highly differentiated when they showed
ample mucin-filled cytoplasm, with or without signet cell configuration, and a regularly
shaped and inconspicuous nucleus. Tumor cells were considered poorly differentiated
when the nucleus to cytoplasm ratio was unfavorable and the nucleus was large, irregularly shaped, and hyperchromatic.

Maximal tumor diameter was recorded on examination of the resected specimens. The resection margins are defined as the surgical resection planes of distal and proximal bile ducts or the liver. The dissection margins constitute the surgical cleavage planes with adjacent hilar structures, such as the portal vein.

Tumor DNA content of the specimens, as assessed in a previous study, was included in this analysis. Diploid or aneuploid tumor status of the long-term survivors, as determined by flow cytometry cell analysis, was recorded.

Postoperative radiotherapy
From 1983 till 1986, only 5 of a total of 17 patients received postoperative (external beam) radiotherapy. Since 1986, all patients routinely receive radiation therapy. Only 7 patients had no radiation therapy after resection due to severe morbidity or refusal of the patient, including one case of a curative resection. Postoperative radiotherapy consisted of a combination of external beam (45Gy) and intraluminal brachytherapy (10.5Gy) in 32 (50%) patients. For brachytherapy, iridium-192 wires were passed intraluminally through the biliary anastomoses. Endoscopical access to the biliary anastomoses was obtained via the distal end of the Roux-Y loop that was brought out for this purpose as terminal jejunostomy. When this was not possible, because of technical reasons, patients were treated with external beam irradiation only, in a higher dose (55Gy). Thus, 13 (20%) patients underwent only external beam irradiation.

Statistical analysis
The chi-square test (the Pearson and the two tails Fisher's exact test) were used to assess the significance of differences between groups. Only probabilities of less than 0.05 were accepted as significant. Survival curves were constructed by the Kaplan-Meier technique.
Results

Of 64 patients, 12 (19%) survived more than 5 years after resection and are termed long-term survivors. There were 7 men and 5 women, with a median age of 59.5 years (range: 21-73). Age and gender were not significantly different among long-term survivors. The long-term survivors group was analyzed taking into account the following characteristics:

Tumor classification and type of resection

Preoperative tumor classification of the 12 long-term survivors as compared to the whole group, was as follows: 3/15 type I (20%), and 9/26 type II (35%). Of the patients preoperatively diagnosed as having a type III (n=17) or a type IV (n=1) tumor, no long-term survivors were included. In 5 patients the preoperative classification was not retrieved.

The definitive Bismuth classification of the tumor as established during operation, differed from the preoperative classification in 3 patients, in which the tumor was upgraded from type II to a type III tumor (table 1). In these patients a hemi-hepatectomy was carried out in combination with hilar resection. Long-term survival did not correlate significantly with the definitive Bismuth classification (p>0.1).

<table>
<thead>
<tr>
<th>Type</th>
<th>Total (n=57)</th>
<th>Long-term survivors (n=12)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>11</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>II</td>
<td>15</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>III</td>
<td>27</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>IV</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*In 7 patients the definitive classification was not retrieved
Concerning the type of resection, nine patients had long-term survival after local resection and three patients after a combination with hemi-hepatectomy. Correlation between long-term survival and type of resection was not statistically significant (p>0.6) (table 2).

<table>
<thead>
<tr>
<th>Type</th>
<th>Total (n=64)</th>
<th>Long-term survivors (n=12)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local resection</td>
<td>51</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>LR+hemi-hepatectomy *</td>
<td>13</td>
<td>3</td>
<td>23</td>
</tr>
</tbody>
</table>

* Five right hemi-hepatectomies (4 extended), and 8 left hemi-hepatectomies (none extended)

**Histopathologic features**

The results of histopathological examination of the specimens of the 12 long-term survivors were compared with the whole group of patients reviewed (table 3 and 4). Tumor multifocality, usually presenting as in situ malignancy, was found in 15 cases (24%). There were no long-term survivors within this group, giving a statistically significant correlation between long-term survival and unifocality of the tumor (p<0.05).

Complete tumor free surgical margins (i.e., both resection and dissection margins) were found in only 4 cases (6%). In 12 patients, the dissection margins were involved but the resection margins were microscopically free of tumor. When considering the resection margins only, the percentage of radical resections would be 25% (16/63), which is more in line with the results reported in the literature. Only 1 of these 4 patients survived for more than 5 years, and died after 75 months due to metastases of a primary ovarian carcinoma.
### TABLE 3. LONG-TERM SURVIVAL IN RELATION WITH HISTOPATHOLOGIC FEATURES (1)

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Total (n=63)*</th>
<th>Long-term survivors (n=12)</th>
<th>%</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologic: high-moderate **</td>
<td>21</td>
<td>2</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Histologic: moderate-poor</td>
<td>41</td>
<td>10</td>
<td>24</td>
<td>0.19</td>
</tr>
<tr>
<td>Cytologic: high-moderate</td>
<td>25</td>
<td>4</td>
<td>16</td>
<td>0.75</td>
</tr>
<tr>
<td>Cytologic: moderate-poor</td>
<td>37</td>
<td>8</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Positive lymphnodes ***</td>
<td>23</td>
<td>4</td>
<td>17</td>
<td>0.75</td>
</tr>
<tr>
<td>Negative lymph nodes</td>
<td>36</td>
<td>8</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Mean tumor size (mm)</td>
<td>18 (4-60)</td>
<td>17 (5-25)</td>
<td></td>
<td>0.65</td>
</tr>
</tbody>
</table>

* One resection specimen could not be retrieved

** One patient with an undifferentiated small cell carcinoma is not included

*** In 4 patients no lymphnodes were found in the histologic specimen.

### TABLE 4. LONG-TERM SURVIVAL IN RELATION WITH HISTOPATHOLOGIC FEATURES (2)

<table>
<thead>
<tr>
<th>Specimen margins</th>
<th>Total (n=63)*</th>
<th>Long-term survivors (n=12)</th>
<th>%</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive liver margin *</td>
<td>20</td>
<td>3</td>
<td>15</td>
<td>0.64</td>
</tr>
<tr>
<td>Negative liver margin</td>
<td>11</td>
<td>3</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Positive dissection margins</td>
<td>55</td>
<td>11</td>
<td>20</td>
<td>1.00</td>
</tr>
<tr>
<td>Negative dissection margins</td>
<td>8</td>
<td>1</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Positive proximal bile duct **</td>
<td>33</td>
<td>3</td>
<td>9</td>
<td>0.04</td>
</tr>
<tr>
<td>Negative proximal bile duct</td>
<td>24</td>
<td>8</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Positive distal bile duct ***</td>
<td>10</td>
<td>1</td>
<td>10</td>
<td>0.67</td>
</tr>
<tr>
<td>Negative distal bile duct</td>
<td>49</td>
<td>11</td>
<td>22</td>
<td></td>
</tr>
</tbody>
</table>

* Only the hemi-hepatectomies and local resections with a partial liver resection (central part lobus IV and/or caudate lobe), (n=31)

** Excluding all resections with liver tissue at the proximal bile duct margin. In 2 patients the proximal bile duct could not be reviewed completely

*** In 4 patients the distal bile duct could not be reviewed completely
In a previous study, tumor DNA analysis was carried out in 46 of all 64 patients included in this study. In 23 cases (50%) the tumor specimen showed a diploid pattern, and this was correlated with improved survival. Tumor ploidy data were available in 8 of the 12 long-term survivors, identified in this study. Seven long-term survivors had diploid tumors and one an aneuploid tumor, showing a statistically significant correlation between diploid tumors and long-term survival (p<0.05).

**Postoperative radiotherapy**

Forty-five patients had postoperative radiotherapy (70%). Thirteen patients had external beam irradiation, four (31%) of whom were long term survivors; 32 patients had a combination of external beam irradiation and brachytherapy and in this group, 6 patients (19%) survived for more than 5 years. Among the 19 patients who did not receive postoperative radiotherapy, there were 2 long-term survivors (11%). Among the four patients with complete tumor-free surgical specimen margins, only one did not receive radiotherapy; this patient was one of the two long-term survivors. There was no statistically significant correlation between long-term survival and postoperative radiotherapy (p>0.35).

**Follow-up**

Complications noted during follow-up are shown in table 5. Only the incidence of ascites was significantly different (p=0.01) when the group of long-term survivors was compared to the rest of the group with complete follow-up. None of the long-term survivors developed ascites.

Of 12 patients, follow-up was not complete concerning the development of metastases or local recurrence. In the group of patients who were suspected of having developed metastases during follow-up, only 8% (three patients, two died) survived more than 5 years, compared to 56% (9 patients), in the group of patients who had no evidence of metastases. One patient died of a metastasis of a second primary tumor, diagnosed as an ovarian adenocarcinoma.
TABLE 5. LONG-TERM SURVIVAL IN RELATION WITH POST-OPERATIVE COMPLICATIONS

<table>
<thead>
<tr>
<th>Complications</th>
<th>Total (n=55)</th>
<th>Long-term survivors (n=12)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periods of cholangitis</td>
<td>31 (56%)</td>
<td>8 (67%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>28 (51%)</td>
<td>5 (42%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Recurrent jaundice</td>
<td>24 (44%)</td>
<td>3 (25%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Ascites</td>
<td>17 (31%)</td>
<td>0 (0%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ileus</td>
<td>16 (29%)</td>
<td>1 (8%)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

* Of nine patients, follow-up was not complete

Of patients with a suspected local recurrence, 12% (two patients) survived for more than 5 years (one died, and one is still alive), compared to 29% (ten patients) in the group of patients without a suspicion of local recurrence. This difference was not statistically significant (p>0.15). In another long-term survivor, who presently is still alive, a primary pancreatic head carcinoma was recently diagnosed. The last of the 5 deceased long-term survivors died of cachexia.

**Survival**

The survival period is calculated until 1996, at the completion date of this study. At this time, there were still seven patients (four men and three women) alive, after 62, 72, 76, 77, 77, 103 and 139 months, respectively. The overall (79 patients) mean survival was 27.4 months (limited to 139.2 months), with a median survival of 15.6 months. The mean survival of the 64 patients analyzed in this study (in which hospital mortality was excluded) was 33.7 months, with a median survival of 18.8 months. The 5 years actuarial survival rate was 15% (fig.1.).
FIGURE 1. KAPLAN-MEIER SURVIVAL CURVE OF 12 PATIENTS WHO SURVIVED MORE THAN FIVE YEARS AFTER RESECTION OF A PROXIMAL BILE DUCT CARCINOMA (KLATSKIN TUMOR). SEVEN PATIENTS WERE STILL ALIVE.

Alive, n=7; at 62, 72, 77, 77, 77, 103, and 139 months
Discussion

In this survival analysis of a series of 64 patients who underwent resection of a Klatskin tumor and did not die during the postoperative period, 12 patients (19%) survived more than 5 years and were called the “long-term survivors”. The objective of this study was to determine prognostic factors for long-term survival in this subset of patients. All of the long-term survivors were preoperatively diagnosed as type I and II, according to the Bismuth classification. In three patients, the tumor appeared to extend into the segmental branches during surgical exploration and therefore, the definitive classification needed to be upgraded. Despite the fact that surgical classification did not significantly correlate with long-term survival, only in these 3 patients with a type III tumor, survival of more than 5 years was achieved after hilar resection in combination with hemi-hepatectomy. Chances for long-term survival, therefore, seem to be better in patients preoperatively diagnosed as type I and II.

Type I and II tumors (confined to the confluence and main hepatic ducts), are usually amenable to local resection although there is much controversy concerning this subject. Pichlmayr et al.1 advocate a combination of local resection and partial liver resection, not only in all tumors of Bismuth type III, but also in type II tumors, because in these cases the rate of radical resections could be enhanced. They argue that in Bismuth type II tumors, extension is usually predominant at one side, being the preferred side for liver resection. Bismuth et al.9, however, recommend in type II tumors, in which the biliary ducts draining the caudate lobe are almost unvariably involved by tumor, that local resection is performed in combination with resection of the caudate lobe. In case of large type II lesions, tumor extension may involve the parenchyma of segment IV, requiring partial resection of segment IV as well. Right or left hemi-hepatectomy seems to be necessary only for type III tumors because of ductal involvement of the secondary bile ducts of the involved side. Although we maintain the latter policy, the chances for long-term survival in this group of patients seems limited (table 1).

Recently, Nakeeb et al.20 showed a median survival of 18 months after a combination
of hepatic lobectomy and extrahepatic bile duct resection, and 19 months after bile duct resection alone. They achieved a 5-year actuarial survival rate of 19% in patients with negative microscopic margins, which was significantly prolonged as compared to a 9% 5-year survival rate in patients with positive margins. Many authors have emphasized that lobar hepatectomy should be added to a local resection, to achieve a higher rate of radical resections, and consequently better survival times. They all, however, achieved 5-year actuarial survival rates of less than 20%. These numbers are not very different from the results of this study (fig. 1) despite the claimed higher curative resection rates (22-57%) compared to the 6% curative resection rate of this analysis. As emphasized in a previous study, examination of the surgical resection planes only, in our opinion, does not provide sufficient information for assessment of radicality of the resection. The surgical dissection (cleavage) planes should be taken into account as well. In the present study, these planes were a major criterion for completeness of the resection, although no significant correlation could be demonstrated between negative surgical dissection margins and long-term survival. Scrutiny of the dissection planes in this study, may explain the discrepancy in percentage of radical resections found in this series, compared to reports in the literature.

Tumor multifocality appeared to be an important, negative prognostic factor, as it was not found within the group of patients who survived for more than 5 years. Among the other tumor characteristics, only the state of the proximal bile duct margin was a prognostic factor, negative margins being related to long-term survival. All other factors, even histological differentiation of the tumor, showed no statistically significant correlation with long-term survival, in contrast to other reports.

In a previous study, tumor DNA analysis of Klatskin tumors showed that diploid tumors were associated with significantly better prognosis after resection. This finding is in keeping with the results of the present study, in which seven of eight evaluable long-term survivors were found to have a diploid tumor.

The role of postoperative radiotherapy in the treatment of resectable Klatskin tumors remains a matter of controversy. Most of the patients of this study underwent
postoperative radiotherapy as part of their protocol.\textsuperscript{30} In an earlier communication, we reported a significant survival benefit of postoperative radiotherapy: patients who had undergone resection without additional radiotherapy had a median survival of 8 (±1.2, SD) months whereas patients with radiotherapy had a median survival of 27 (±5.5, SD) months.\textsuperscript{30} Although 10 of 12 long-term survivors underwent postoperative radiotherapy, postoperative irradiation in this study did not significantly contribute to long-term survival. However, as we reported previously\textsuperscript{18}, the beneficial effect of radiotherapy was apparent only in patients with aneuploid Klatskin tumors, providing a possible explanation why radiotherapy was not found to be a significant factor in the long-term survival group in which tumors were mainly diploid.

Seventy percent of 52 evaluable patients (after exclusion of the deceased patients due to postoperative complications and the twelve patients with insufficient follow-up data), had a suspicion of metastases during follow-up. Of the long-term survivors, however, metastatic disease was suspected in only 3 (25%) patients.

In conclusion, among 64 patients who had undergone resection for a Klatskin tumor in this analysis, 12 (19%) patients survived longer than 5 years. Bismuth type I and II classification, absence of multifocality, diploid tumors, and negative proximal bile duct margins at histopathological examination, were all significant prognostic factors for long-term survival.

\section*{Acknowledgements}

The authors wish to thank N.J. Lygidakis, M.D., and M.N. van der Heyde, M.D., for their contributions to the series of patients described in this study. The data presented in this study are part of a recent, re-evaluation of all patients operated for a proximal bile duct carcinoma between 1983 and 1996, and may differ from data quoted in previous communications.
References


CHAPTER 9 LONG-TERM SURVIVAL AFTER RESECTION OF PROXIMAL BILE DUCT CARCINOMA 189


