Hepatic resections in the treatment of hilar cholangiocarcinoma (Klatskin tumor)

Ph. D thesis’ abstract

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Iaşi, 2011
General Part

1. Introduction
Colangiocarcinoma (CC) is a tumour developed from biliary epithelium duct.

Those interesting biliary confluence or hilar cholangiocarcinoma (CCH) were firstly described by Gerald Klatskin in 1965 and received afterwards this eponym.

During last three decades surgical treatment for CCH changed dramatically, becoming more aggressive with better results regarding patients’ survival. This has been obtained performing hepatic resections besides bile duct excisions.

2. Epidemiology
CC, both intra and extra hepatic, represents 3% of the gastrointestinal cancers. Of those extrahepatic, CCH represents 40 to 60% in the series reported.

3. Natural history
The majority of the untreated patients dies within 6 to 12 months from the moment of diagnosis by hepatic failure or infectious complications due to biliary obstruction.

4. Pathology
The synonyms describing the same entity are: proximal biliary cancer, cancer of the biliary confluence, malignant stenosis of the biliary confluence, hilar cholangiocarcinoma, Klatskin tumour.

CCH are mainly adenocarcinoma. Non-epithelial tumours are rarely encountered: carcinoid, sarcoma, lymphoma, metastases from another primary cancer (colorectal).
5. Local, regional and systemic evolution

The original article of Klatskin and the following ones evidenced the progression of extra hepatic biliary tumours is very slow. The extension is local and regional. Neural invasion is constant and the regional extension is towards the lymphatic nodes of the hepatic pedicle, portal vein and liver parenchyma.

Metastases, with the exception of those in the liver, are exceptional.

6. Symptoms and clinical exams

The symptoms are not specific. There are three main categories of clinical aspects:

1) biliary obstruction: jaundice, pain in the right upper quadrant, nausea, pruritus
2) general symptoms: anorexia, loss of weight, asthenia
3) signs and symptoms of metastatic disease: fatigue, lethargy, loss of weight.

7. Staging and classification systems

First classification was proposed in 1975 by Henri Bismuth and Marvin B. Corlette; in a modified form it is largely used today.

Bismuth-Corlette classification

<table>
<thead>
<tr>
<th>Type I: tumour invades biliary confluence but right and left channels communicate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type II: tumour invades biliary confluence and right and left channels do not communicate</td>
</tr>
<tr>
<td>Type III: tumour invades biliary confluence and extend on hepatic channels</td>
</tr>
<tr>
<td>IIIa: extension on right hepatic channel</td>
</tr>
<tr>
<td>IIIb: extension non left hepatic channel</td>
</tr>
</tbody>
</table>
Type IV: tumor is either multicentric or invades right and left hepatic channels

The most used system is the TNM (tumour, nodes, metastases) proposed by UICC (Union Internationale Contre le Cancer).

The last edition (January 2010) introduces for the first time the split of extra hepatic biliary cancers in proximal (including CCH) and distal. It also changes some aspects of T and N categories and eliminates Mx from all stages of solid tumours.

**Staging of proximal extra hepatic biliary cancers**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2a-b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T1-3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

**8. Diagnosis**

CCH are silent for long periods. Jaundice is the prominent symptom and is, usually, progressive and unremitting.
8.1 Imagistic diagnosis
Radiologic studies are essential in the management of patients with CCH, during the last decade, the selection of them changed dramatically. MRI, MRCP and cholangio-MRI are the first choice.

8.2 Diagnostic laparoscopy
Laparoscopic staging is used to identify the patients with metastatic disease in which surgical operation with curative intent is not possible.

8.3 Differential diagnosis
Includes: lymphatic nodes metastases, intrahepatic cholangiocarcinoma with hilar extent, lymphoma, lythiasis of the main hepatic duct, Mirizzi syndrome, granuloma, benign fibrosis, tuberculosis, traumatic sequels, retroperitoneal fibrosis.

9. Preoperative management
It is very important to have a good functioning liver after surgery. For this and to increase curability, there were developed techniques such as preoperative biliary drainage and portal vein embolization.

Surgeon must assess resectability because only the resection represents an effective therapy.

Criteria for non-resectability include:
- Infiltration beyond second biliary branches in both hemilivers;
- Invasion of the great vessels (portal vein or hepatic artery), invasion of the right and left branches of the portal vein, invasion of a branch of the portal vein and of the contralateral hepatic;
- Vascular invasion on one side and contralateral biliary invasion;
Lymphatic invasion beyond N1 stations

10. Surgical options and techniques

10.1 Surgical anatomy

In the middle of the twentieth century, the French anatomist Claude Couinaud described segmental anatomy of the liver, based on the intrahepatic distribution of the vessels. Couinaud’s classification of the hepatic anatomy divides the liver in eight independent functional segments, each having its own biliary, arterial and portal triad.

10. 2 Curative surgical options

Surgical treatment of CCH has three objectives: complete tumoural excision with negative histological margins, removal of the symptoms related to biliary obstructions and the bilioenteral restoration.

Surgical strategy is based on the peroperative exploration, including peroperative ecography.

Curative surgical options are:
1. Bile duct resection
2. Hepatic and bile duct resection
3. Combined hepatic and vascular resection
4. Hepatopancreatoduodenectomy
5. Liver transplantation

11. Postoperative complications

Japanese and American authors speak about minor and major complications while European authors classify them as immediate and late complications.

The rate of major complications varies between 33 and 50% in the majority of the series published.
12. Prognostic factors for survival after resectional surgery for CCH

Many studies demonstrated survival of the patients after surgery for CCH depends on some clinical and pathological factors.

The most of them stated the negative impact on survival of the: perineural invasion, lymphatic nodes invasion, involved resected margins, vascular invasion, male gender, low tumoral grading, absence of the caudate lobe resection, presence of the lobar atrophy.
CHAPTER I

AIM OF THE STUDY

Klatskin tumors represent a rare pathology encountered in clinical practice. In the last two decades grew significantly the number of series reported and changed dramatically their management.

Surgery offers the only chance for cure and here emerged the need for hepatic resection for better results.

I worked during 2003 and 2005 in Rennes, France in a hepatic surgical service. Professor Karim Boudgema, chief of the service proposed me to make a research on the surgical treatment of hilar cholangiocarcinoma during the period 1994 to 2004.

CHAPTER II

STATISTIC METODOLOGY

It was used STATISTICA for medical research program. Were applied various tests for analysis (ANOVA, Scheffé, Spjotvol/Stoline), and specific tests of correlation for variables (Pearson, CHI – pătrat ($\chi^2$), Mantel-Haenszel, Fisher, Spearman, Kendall tau ($\tau$), Gamma) etc.
CHAPTER III
MATERIAL AND METHOD

For the study were retrospectively consulted the database and archive of the Digestive Surgery service of CHU (Centre Hospitalier Universitaire) of Rennes, France. There were 62 patients treated for Klatskin tumors from 01 January 1994 to 31 July 2004. 56 patients were operated on, 33 patients with curative intent and 23 of them underwent palliative operations.

The study was performed on the 33 patients operated on with curative intent (resectability of 59%).

Patients were grouped in two categories, according to the type of surgery:

1) 7 patients in which was performed resection of the extrahepatic bile duct (RCBEH)
2) 26 patients in which was performed a hepatic associated resection (RHA) besides RCBEH, more or less extended, with or without resection of the segment 1 (caudate lobe).

<table>
<thead>
<tr>
<th>Type of intervention</th>
<th>No. of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCBEH &amp; RHA</td>
<td>26</td>
<td>78.79%</td>
</tr>
<tr>
<td>RCBEH</td>
<td>7</td>
<td>21.21%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>33</strong></td>
<td></td>
</tr>
</tbody>
</table>

There is a slight male gender predominance, not significant statistically.
<table>
<thead>
<tr>
<th>Type of intervention</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>RCBEH</td>
<td></td>
</tr>
<tr>
<td>RCBEH &amp; RHA</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>RCBEH</th>
<th>RCBEH &amp; RHA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>2</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>15.38%</td>
<td>84.62%</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>25.00%</td>
<td>75.00%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>26</td>
<td>33</td>
</tr>
</tbody>
</table>

Diagram: Felul interventiei vs. sexe
- Masculin: 25.0% RCBEH, 75.00% RCBEH & RHA
- Feminin: 15.4% RCBEH, 84.62% RCBEH & RHA
CHAPTER IV

RESULTS

Patients who underwent RCBEH associated more frequently pruritus ($\beta=0.62$, $p=0.009$), anorexia ($\beta=0.79$, $p=0.0073$) and weight loss ($\beta=5.16$, $p=0.0071$).

Some biological values were analysed (haemoglobin, haematocrite, alkaline phosphatases, aspartat amino-transpherase (ASAT), alanil amino-transpherase (ALAT), total and direct bylirubinaemia).

Medium values of alkaline phosphatases and medium values of ASAT and ALAT were significantly lower in patients receiving RCBEH as treatment.

Medium values of total and direct bylirubinaemia were significantly lower in the group receiving RCBEH and RHA as treatment.

Bismuth-Corlette staging
RCBEH was the surgical option for all the cases classified Bismuth-Corlette type I. RCBEH and RHA was applied in Bismuth-Corlette type II, III and IV.

**TNM staging**

For the N factor were modified N2 lymph nodes into N1 according to the last definition in UICC seventh edition.
The analysis of the TNM staging in relation with operations performed showed:

1. Referring to T factor
There is a significant association between the type of surgery and T factor ($\chi^2=7.79$, $p=0.02$, $r=-0.904$, 95%CI).

2. Referring to N factor

Hepatic associated resections
Extension of hepatectomy (number of resected segments)

Type of resection (R0, R1)

The resected margins were found invaded in 33% of cases.
Resection of the segment 1 (caudate lobe)

Length of the operations
RCBEH and RHA are significantly longer than RCBEH.

**Arterial invasion**
Portal invasion

Perineural invasion
Lymph nodes invasion

Tumoral vascular embolia
Peroperative transfusions
Postoperative transfusions

Postoperative complications, reoperations
There is a strong correlation between complications and the group with RCBEH and RHA. The risk of complications is 8.33 bigger in this group.

**Postoperative deaths**

![Postoperative deaths chart]

**Length of hospital stay**
Analysis of factors influencing survival

Survival in group RCBEH & RHA
Survival in group RCBEH
Influence of caudate lobectomy
Categ. Box & Whisker Plot: supraviețuire
supraviețuire: $F(1,50) = 2.6911, p = 0.004097$;
Kruskal-Wallis-H(1,52) = 0.9148, p = 0.3388

<table>
<thead>
<tr>
<th>Category</th>
<th>Mean</th>
<th>Mean±SE</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>absenta</td>
<td>15.82</td>
<td>19.54</td>
<td></td>
</tr>
<tr>
<td>prezenta</td>
<td>19.54</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rezectia segmentului 1

Cumulative Proportion Surviving (Kaplan-Meier)

Include condition: Rezectia segmentului 1

Cumulative Proportion Surviving (luni)
Influence of vascular invasion
Influence of portal invasion

SUPRAVIŢUIRE

39.13% 10.00%
60.87% 90.00%

ÎN VIATĂ DEȘEDĂȚI
Influence of perineural invasion
Influence of lymph nodes invasion
Invazia ganglionilor limfatici

Prezentă
- 75.00%
- 25.00%

Absență
- 66.67%
- 33.33%

Include condition: interventie chirurgicala

Cumulative Proportion Surviving (Kaplan-Meier)

- Complete
- Censored

Include condition: interventie chirurgicala
Influence of complications

Complicații vs. deceze

Prezente
77.3%  22.7%

Absente
54.6%  45.5%

Cumulative Proportion Surviving (Kaplan-Meier)
Include condition: interventie chirurgicala

Cumulative Proportion Surviving (Kaplan-Meier)

Include condition: interventie chirurgicala
Analysis of the signs and symptoms as predictive factors of the outcome

Complications vs. signs and symptoms
Mortality vs. signs and symptoms
The most important sign correlated to patients’ death was weight loss.

Length of hospital stay vs. signs and symptoms

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Medium length of stay</th>
<th>Media -95%</th>
<th>Min</th>
<th>Max</th>
<th>Q25</th>
<th>Q75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td>22.50</td>
<td>18.94</td>
<td>5.00</td>
<td>64.00</td>
<td>13.00</td>
<td>28.00</td>
</tr>
<tr>
<td>Pain</td>
<td>20.09</td>
<td>14.71</td>
<td>5.00</td>
<td>50.00</td>
<td>12.00</td>
<td>24.00</td>
</tr>
<tr>
<td>Nausea</td>
<td>23.20</td>
<td>11.84</td>
<td>5.00</td>
<td>50.00</td>
<td>14.00</td>
<td>24.00</td>
</tr>
<tr>
<td>Weight loss</td>
<td>22.00</td>
<td>17.86</td>
<td>11.00</td>
<td>50.00</td>
<td>12.00</td>
<td>32.00</td>
</tr>
<tr>
<td>Asthenia</td>
<td>24.36</td>
<td>16.67</td>
<td>11.00</td>
<td>64.00</td>
<td>12.00</td>
<td>32.00</td>
</tr>
<tr>
<td>Anorexia</td>
<td>18.67</td>
<td>15.25</td>
<td>12.00</td>
<td>25.00</td>
<td>12.00</td>
<td>23.00</td>
</tr>
<tr>
<td>Feverus</td>
<td>22.00</td>
<td>3.63</td>
<td>12.00</td>
<td>32.00</td>
<td>12.00</td>
<td>32.00</td>
</tr>
<tr>
<td>Prurit</td>
<td>23.30</td>
<td>18.15</td>
<td>5.00</td>
<td>64.00</td>
<td>12.00</td>
<td>29.00</td>
</tr>
</tbody>
</table>
Surgical treatment of CCH has dramatically changed in the last two decades. Complete surgical resection is now achieved through aggressive approach, including extended hepatectomies.

This retrospective study reports on a series of 33 patient operated on with curative intent from 01 January 1994 to 31 July 2004 in Digestive Surgical Service of Centre Hospitalier Universitaire in Rennes, France. 26 of them had RCBEH and RHA and 7 patients had only RCBEH.

Statistical research looked for factors which could influence postoperative outcome or survival.

Patients in the group having RCBEH as operation had preoperatively jaundice, anorexia and weight loss more frequently when compared to the other group.

From the laboratory values were statistically significant total and direct bilirubinaemia (bigger values in the group with RCBEH) and alkaline phosphatases, ALAT and ASAT, with bigger values in the group with RCBEH and RHA.

Bismuth-Corlette staging evidenced almost half of the cases belonged to type III.

TNM staging showed 20 cases T2 and there were no cases staged T4. N factor was N1 (metastases in regional lymph nodes) in 12 patients. T factor was correlated with the type of resection.

Resectability was 58.9%; cases staged Bismuth/Corlette type I (7 patients) received RCBEH and the other types RCBEH and RHA. In 25 patients from this later group were performed major hepatectomies.

The operations were significantly longer when hepatectomy was associated.
Negative margins were obtained in 22 patients. In the group with RCBEH negative margins had 42.86% of the patients while in the other group the percentage was 73.08. This was statistically significant.

Lymph nodes were found involved in 36.36% of the patients. Survival was significantly shorter in these cases.

Resection of the caudate lobe (segment 1) was done in 20 patients, survival being slightly better in these cases.

Portal ipsilateral invasion was found in 30% of the patients, in this group survival being significantly worse.

Arterial invasion was 27.27%, survival being slightly worse in these cases.

Perineural invasion was found in 24 of the patients. There was no significant difference regarding survival.

Morbidity was 66%, including minor and major complications. When only major complications were taken, morbidity came down to 19%, all appearing in the group with RHA.

Statistics showed interesting correlation between preoperative signs and symptoms and complications. Patients having jaundice, nausea, anorexia or pain were more probably to have complications in their postoperative outcome.

Mortality was 15.15% (5 cases), all in the group with RHA. Weight loss preoperatively was a predictive factor for death.

Length of hospital stay was significantly shorter in patients with anorexia and longer in the group with RHA. Preoperative transfusions were 4 times more frequent in the patients with RHA.
CHAPTER VII
CONCLUSIONS

This study confirmed aggressive approach in patient with Klatskin tumours is justified to obtain cure, morbidity and mortality being acceptable. The following aspects were retained:

1. Patients which received RCBEH as treatment had more frequently jaundice, anorexia and weight loss.
2. It was a significant differences for total and direct bylirubinaemia (bigger values in the group with RCBEH) and alkaline phosphatases, ALAT and ASAT, with bigger values in the group with RCBEH and RHA.
3. Half cases were Bismuth-Corlette type III and RCBEH was applied only for Bismuth-Corlette type I.
4. TNM staging showed there was a correlation between T factor and the type of resection.
5. From 26 cases with RHA, in 25 were performed major heptectomies. Curative resection was more frequently obtained when segment 1 was resected, survival being better.
6. Curative resection (R0) was obtained more frequently in the group with RHA.
7. Survival was better when was no arterial, portal or lymph nodes invasion.
8. Interesting correlation was found between preoperative signs and symptoms and complications; there were more complications when jaundice, nausea, anorexia or pain were present. It also has been found weight loss predicted death.
9. Morbidity and mortality rates were similar to literature. It was significantly more complications in the group with RHA.

In conclusion, in patients with Klatskin tumours, surgery has to associate heptectomies and segment 1 resection. When this is correctly indicated and performed by experienced teams, this
brings benefits in terms of survival and constitutes nowadays standard for the surgical treatment for the majority of patients.

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