**Name of Journal: *World Journal of Gastrointestinal Surgery***

**ESPS Manuscript NO: 24638**

**Manuscript Type:** **Original Article**

***Retrospective Study***

**Predictors of long term survival after hepatic resection for hilar cholangiocarcinoma: 5-year survivors retrospective study**

**Abd ElWahab****M** *et al.* 5-year survivors after hepatic resection for HCC

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**Institutional review board statement:** This study was approved by institutional review board of Mansoura University.

**Informed consent statement:** Informed consent was obtained from all patients to undergo surgery after a careful explanation of the nature of the disease and possible treatment with its complications.

**Conflict-of-interest statement:** No conflict of interest.

**Data sharing statement:** No data sharing.

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**Received:** January 30, 2016

**Peer-review started:** January 31, 2016

**First decision:** March 23, 2016

**Revised:** March 26, 2016

**Accepted:** April 14, 2016

**Article in press:**

**Published online:**

**abstract**

**Aim:** to determine predictors of long term survival after resection of Hilar cholangiocarcinoma (HC) and to compare patients surviving more than 5 years with patients who survived less than 5-years.

**methods:** This is a retrospective study of patients with pathologically proven HC who underwent surgical resection in the Gastoenterology surgical center, Mansoura University, Egypt between January 2002 and April 2013. All data of the patients were collected from the medical records. Patients were divided into two groups according to their survival; less than five year survivors and more than five year survivors.

**Results:** There were 34 (14%) long term survivors (5 year survivors) among a 243 patients. Five-year survivors were younger at diagnosis than those surviving less than 5 years with a mean age (50.47 ± 4.45 versus 54.59 ± 4.98, *P* = 0.001). Gender, clinical presentation, preoperative drainage, preoperative serum bilirubin, albumin and SGPT were similar in both groups. The level of CA 19-9 was significantly higher in < 5-year survivors group (395.71 ± 31.43 *vs* 254.06 ± 42.19, *P* = 0.0001). Univariate analysis demonstrated nine variables to be significantly associated with long term survival > 5 year including; young age (*P* = 0.001), serum CA19-9 (*p* = 0.0001), non cirrhotic liver (*p* = 0.02), major hepatic resection (*p* = 0.001), caudate lobe resection (*p* = 0.006) , well differentiated tumour (*p* = 0.03), lymph node status (0.008), R0 resection margin (p=0.0001) and early postoperative liver cell failure (*p* = 0.02).

**Conclusion:** Liver status, resection of caudate lobe, Lymph node status, R0 resection and CA19-9 were demonstrated to be independent risk factors for long term survival.

**Key words:** Hilar cholangiocarcinoma; hepatic resection; caudate lobe resection**;** CA19-9; liver cell failure

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**Core tip:** Hilar cholangiocarcinoma (HC) is an uncommon malignancy with a relatively poor prognosis. Surgery remains the only line of treatment offering the possibility of cure. The central location of the tumor and its close relationship to vascular structures at the hepatic hilum have resulted in a low resectability rate. Five year survivors were younger at diagnosis than those surviving less than 5 years. Major hepatic resection and caudate lobe resection achieved better R0 resection rate. Liver status, resection of caudate lobe, Lymph node status, R0 resection and CA19-9 were demonstrated to be independent risk factors for long term survival.

Abd ElWahab M, El Nakeeb A, El Hanafy E, Sultan AM, Elghawalby A, Askr W, Ali M, Abd El Gawad M, Salah T. Predictors of long term survival after hepatic resection for hilar cholangiocarcinoma: 5-year survivors retrospective study. *World J Gastrointest Surg* 2016; In press

**Introduction**

Hilar cholangiocarcinoma (HC) is the most common type of biliary tract malignancy, arising at the confluence of the right and left hepatic ducts and comprise 40% to 60% of all cholangiocarcinoma[1-3]. It is a complex and aggressive disease with poor prognosis[2-6]. The resectability rate varies from 25% to 58% of patients who are surgically explored due to locally advanced tumour, or liver metastasis. The central location of the tumor and its close relationship to vascular structures at the hepatic hilum have resulted in a low resectability rate and high morbidity and mortality[3-7].

Although the results of surgical treatment for HC were dismal, recent studies have reported improved outcomes using aggressive surgical approaches, postoperative morbidity generally ranges from 30% to 50% and mortality is 10% or less[5-10]. However, the actual 5-year survival after radical resection of HC ranges from 10% to 28 % with the majority of studies reporting 20% or higher. The median survival after curative resection is about 19 to 35 mo[10-13].

Few studies of HC have long enough followed up to report a survival beyond 5 years[7-10]. It has long been recognized that radical resection offers the only hope for cure and improves long term survival. Many studies have confirmed that hepatic resection combined with caudate lobe resection can achieve higher rates of margin-free resection (R0) and significantly improve the overall survival[4-6,11-15].

The aim of this study is to determine variables that are predictors of long term survival after resection of HC and to compare patients surviving 5-years after resection of HC with patients who survived less than 5-years.

**Materials and methods**

This is a retrospective study of patients with pathologically proven HC who underwent surgical resection in the Gastoenterology surgical center, Mansoura University, Egypt between January 2002 and April 2013. Data were collected from the patient records April 2015. Follow up was held regularly at the outpatient clinic. The patients were treated in accordance with the center policy as patients with liver metastasis, lymph node metastasis far beyond regional lymph nodes and local vascular invasion of the major vessels of the contralateral site considered unresectable tumour.

Informed consent was obtained from all patients after a careful explanation of the nature of the disease and possible treatment with its complications. The study was approved by the Institution review board (IRB).

Patients were divided into two groups according to their survival: less than five year survivors and more than five year survivors.

***Preoperative assessment***

All patients underwent full laboratory investigations, abdominal CT with contrast and/or magnetic resonance cholangiopancreatography (MRCP). Upper Gastrointestinal tract (GIT) endoscopy was done routinely to exclude esophageal and fundic varices. Preoperative biliary drainage was done by endoscopic retrograde cholangiopancreatography (ERCP) or by Ultrasound (US) guided percutaneous transhepatic drainage to improve the general condition of the patient before surgery especially if there was cholangitis. The state of the liver and the extent of cirrhosis was assessed by modified Child-Turcotte-Pugh (CTP) classification[16].

***Surgical procedure***

Exploration was done by a bilateral subcostal incision with midline extension of the incision in some cases. Evaluation of the tumour, liver condition and the extent of lymphatic spread were done at first. The choice of surgical procedures depended on tumour extension and general condition of the patients. The tumours extension was classified according to the Bismuth-Corlette classification system[17]. All hepatobilliary resections were performed with the intent of achieving free safety margin (R0). Proximal and distal margins were assessed on frozen section during the operation in some cases. If safety margin was proved to be positive, addition hepatobiliary resection was done as far as technically feasible until R0 was obtained if possible.

All cases underwent extrahepatic biliary resection and lymphadenectomy of locoregional lymph nodes starting from the celiac trunk up to the hilum enbloc with the mass. Hepatic resection was variable from minor resection, which included three or less segments to major resection, which included four or more segments according to Couinaud nomenclature. Hepatic resection was done by harmonic scalpel with or without Pringle`s maneuver to control bleeding. Biliary anastomosis was done by hepaticojejunostomy with or without stenting.

Localized resection (minimal central hepatectomy segment 4) was performed in patients with type I HC without any evidence of hepatic infiltration nor lymph node metastases, cirrhotic liver, and poor general condition. Hemihepatectomy was selected in cases of single lobe atrophy, invasion of the its portal or hepatic branches or extension of the tumor up to the parenchyma of that lobe. Caudate lobe resection was also done in the majority of cases within the last five years.

***Postoperative management***

After surgery, patients were admitted to the intensive care unit (ICU) in the early postoperative days to receive the usual postoperative care by the same surgical teams.

Liver function tests were measured on postoperative period regularly on the first, third day and on the day of discharge. Abdominal ultrasonography was done routinely to all patients and repeated when there were complications. Tube drainage was carried out to any significant abdominal collections.

All pathological reports were reviewed to determine the extent of the tumour, differentiation, lymph node infiltration and positive resection margin. R0 resection was defined as cases in which no gross or microscopic tumour residue was left behind, R1 resections had microscopically positive margins and R2 resections still contained some gross tumor matter[18]. Hospital mortality was defined as death during the first 30 postoperative days.

***Follow up***

Follow up was done in the outpatient clinic at 1 month, 6 months, and then every year. Clinical examination, routine laboratory investigations (complete liver function, complete blood picture and tumour markers CEA and CA 19-9), abdominal sonography and CT scans were done at each visit.

***Data collection***

Preoperative clinical data, intraoperative and postoperative data were collected. Postoperative complications, survival rates and recurrence rates were noted and recorded.

***Statistical analysis***

Statistical analysis of the data in this study was performed by SPSS software, version 17 (Chicago, IL, United States). Descriptive data were expressed as means with standard deviation. Categorical variables were described using frequency distributions. Independent sample t-test was used to detect differences in the means of continuous variables and Chi square test was used in cases with low expected frequencies. *P* values < 0.05 were considered significant. Variables with *P* < 0.05 were entered into the Cox regression model to determine independent factors of 5 year survivors. The independent factors of the variables were expressed as odds ratios (OR) with their 95% confidence intervals (CI). Survival curves were done using Kaplan-Meier method and differences in survival curves were compared with a cox-regression analysis.

**Results**

Between January 2002 and April 2013, surgical intervention with curative intent were performed on 278 patients who had HC. Eventually, 243 patients underwent hepatobiliary resection and 35 did not undergo any resection because of advanced disease (liver metastasis in 11 cases, local vascular infiltration in 24 cases). Of these, 34 (14%) patients were long term survivors (> 5 years) and 209 (86%) were short term survivors (< 5 years). In this study 1 , 3 and 5 year survival rates were 53%, 35% and 22% respectively and the median survival was 24 mo.

Five-year survivors were younger at diagnosis than those surviving less than 5 years with a mean age (50.47 ± 4.45 versus 54.59 ± 4.98, *P* = 0.001). Gender, clinical presentation, preoperative drainage, preoperative serum bilirubin, albumin and SGPT were similar. The level of CA 19-9 was significantly higher in < 5-year survivors group (395.71 ± 31.43 *vs* 254.06 ± 42.19, *P* = 0.0001) (Table 1).

Intraoperative data are shown in (Table 2). Major hepatectomy, including right or left hepatectomy was carried out in 173 (71.19%) of 243 patients besides 70 (28.8%) patients who underwent localized resection. The extent of hepatic resection had a significant impact on the survival rate. Major hepatobiliary resection was performed in 30 )88.23%) patients in > 5-year survivors group and in 143 (68.42%) in < 5 year-survivors group. The segment I resection was done in 23 (67.64%) patients with survival > 5 years and it represents a significant factor in long term survival (*p* = 0.006). Liver status represented a significance difference in both groups. Five-year survivors had a less cirrhotic liver than those surviving less than 5 years (0.02).

The postoperative data are shown in Table 3, five-year survivors had a well differentiated tumors than those surviving less than 5 years [18 (52.4%) *vs* 78 (37.32%). *P* = 0.033]. In addition, 5-year survivors were less likely to have positive lymph nodes [6 (17.6%) *vs* 81 (41.8%) *p* < 0.008] and positive resection margin (R1) [6 (17.6%) *vs* 116 (56.7%), *P* = 0.0001] (Figure 1).

Hepatic recurrence occurred in 51 (24.4%) patients in < 5 years survival group, 40 of them (78.4%) had R1 while hepatic recurrence occurred in 8 (23.52%) patients in > 5 years survival group, 4 of them (50%) had R1.

Univariate analysis demonstrated nine variables (Young age, serum CA19-9, non cirrhotic liver, major hepatic resection, resection of caudate lobe, well differentiated tumour, lymph node status, R0 resection margin and early postoperative LCF) to be significantly associated with long term survival > 5 years. These nine factors identified in univariate analysis were further analyzed in multivariate analysis. Liver status, resection of caudate lobe, lymph node status, R0 resection and serum CA19-9 were demonstrated to be independent risk factors for long term survival Table 4.

**Discussion**

Cholangiocarcinoma is an uncommon malignancy with a relatively poor prognosis providing a major therapeutic challenge. Surgery remains the only line of treatment offering the possibility of cure, but it remains difficult because of their proximity to and possible local vascular infiltration including portal vein, hepatic artery and the surrounding liver parenchyma and caudate lobe[4-7,19-22]. The management and surgical approach for HC has changed in the last two decades from primairly minor surgeries to major hepatectomy with CBD resection and portal vein resection. Now all experienced hepatic surgeons agree to do hepatic resection with the extrahepatic biliary tree when treating HC[20-26].

The resectability rate of HC varies in different studies from 20% to 80%. The actual 5- year survival after radical resection of HC ranges from 10 to 28% with the majority of studies reporting 20% or higher[10-15,20-26]. In this study 1, 3 and 5 year survival rates were 53%, 35% and 22% respectively. The median survival for these cases was 24 months. Thirty four (14%) patients were long term survivors (more than five years) and 209 (86%) were short term survivors (< 5 years). Five-year survivors were younger at diagnosis than those surviving less than 5 years with a mean age (50.47 ± 4.45 *vs* 54.59 ± 4.98, *P* = 0.001).

The role of preoperative biliary drainage (PBD) in the management of HC remains controversial. But, no evidence that routine PBD facilitate resection, decrease postoperative morbidity or increase survival rate[27,28]. Although PBD didn't represent a significant factor affecting long term survival, it is mandatory in cases of preoperative cholangitis, bad general condition and it improves the postoperative course of patients with serum bilirubin level more than 20 mg/dl[15,26].

Curative surgery for patients with HC often necessitates hepatic resection to achieve a R0 resection and improve the long term survival because the characteristics of its growth pattern include longitudinal intraductal extension, perineural, lymphatic route and direct liver invasion[6-9,20-26]. Major hepatic resection is considered the curative treatment of HC, but it is not always safe because postoperative liver cell failure is a common cause of death after major resection in patients with compromised liver function. But the dilemma between major hepatic resection with potential postoperative hepatic cell failure and localized resection with potential R1 and R2 resection margins might be solved by advances in preoperative and intraoperative assessment[15]. Recent advances in perioperative and operative techniques, instruments and care have led to marked improvement in short and long term outcomes after major hepatic resection[15]. Major hepatobiliary resection for HC improve survival rate which provides R0 resection. In this study, 88.23% of > 5-year survivors underwent major hepatic resection.

As the caudate lobe is infiltrated by HC either directly due to the close anatomic relationship or by invading the biliary branches, routine caudate lobe resection should be performed for curative treatment of HC[15,29-31]. Better R0 resection rate and long term survival are achieved by caudate lobe resection in treating cases of HC[15,29-34]. Nimura et al found that 98% of caudate lobe resection were pathologically confirmed to be tumour positive in cases of HC[33]. However, other authors showed that the caudate lobe was infiltrated by HC in 25%-40% of cases[15,33-35]. Segment 1 resection represents a significant factor affecting survival (*P* = 0.006) in our study. In the initial period of the study Caudate lobe resection was performed only when infiltrated, but now it is performed routinely in all cases of HC.

Safety margins after hepatic resection for cholangiocarcinoma represented a highly significant factor affecting long term survival. Many authors have reported a negative surgical margin (R0) to be an important prognostic variable. R0 resection rate in literatures varies from 14 to 80 % and overall 5-year survival for R0 resection were 22 to 45%[4-7,15-17,26-30]. The frequency of R0 resection depends on extent of hepatic resection. To obtain R0 resection, removal of caudate lobe resection is required because of the high rate of infiltration (30%-39%)[15,29-33]. In the current study five-year survivors were less likely to have a positive safety margin [6 (17.6%) *vs* 116 (56.7%), *P* = 0. 0001]. Surgical treatment of HC with localized resection has been shown to result in early recurrence after surgery due to positive surgical margins at the hepatic edge of the bile duct with short, long term survival[4-8,15,26-30,32, 36-40].

Lymph node metastasis is present in 20-50% of cases of cholangiocarcinoma in previous literature[5-12,20-25,32,35-41]. When no lymph node metastasis were detected, the 5-year survival was more than 60%. In contrast, in patients with lymph node metastasis, the 5 year survival was only 21%[25,26]. Lymph node metastasis beyond the hepatoduodenal ligament (celiac, mesenteric LN, or PALN) has a poor prognosis with a 5-year survival less than 12%, so it is considered a contraindication to resection.

Cirrhosis are expected to be associated with increased blood loss, need for blood transfusion and increased post-hepatectomy LCF. The treatment of HC needs careful patient selection, good perioperative assessment and care, and good decision on the extent of hepatobiliary resection. This can be explained to carry out the localized resection in cirrhosis and so the achievement of R0 is less in cirrhotic patients with HC[4-7,32,38-42]. In the current study, five-year survivors had a less cirrhotic liver than those surviving less than 5 years. This result in cirrhotic patients is attributed to; HC more aggressive, localized resection without caudate lobe resection is more applicable and poor liver reserve. This can explain the worse 5-year survival in cirrhotic patients in comparison to non-cirrhotic patients[5,30,39,42].

In conclusion, the 5-year survivors with resected HC are 34 (14%) patients. Five year survivors were younger at diagnosis than those surviving less than 5 years. The majority of long term survivors after resection of HC underwent major hepatic resection and caudate lobe resection. Well differentiated HC tumour, negative surgical margins and negative nodal metastasis have an impact on long term survival after hepatic resection for cholangiocarcinoma.

**COMMENTS**

***Background***

Hilar cholangiocarcinoma (HC) is an uncommon malignancy with a relatively poor prognosis. HC is the most common type of biliary tract malignancy, arising at the confluence of the right and left hepatic ducts and comprise 40% to 60% of all cholangiocarcinoma. Surgery remains the only line of treatment offering the possibility of cure, but it remains difficult. The actual 5-year survival after radical resection of HC ranges from 10% to 28%. The median survival after curative resection is about 19 to 35 mo.

***Research frontiers***

Few studies of HC have long enough followed up to report a survival beyond 5 years. It has long been recognized that radical resection offers the only hope for cure and improves long term survival. Many studies have confirmed that hepatic resection combined with caudate lobe resection can achieve higher rates of margin-free resection (R0) and significantly improve the overall survival

***Innovations and breakthroughs***

The management and surgical approach for HC has changed in the last two decades. Now all experienced hepatic surgeons agree to do hepatic resection with the extrahepatic biliary tree when treating HC. Curative surgery for patients with HC often necessitates hepatic resection to achieve a R0 resection and improve the long term survival because the characteristics of its growth pattern include longitudinal intraductal extension, perineural, lymphatic route and direct liver invasion.

***Applications***

 The data in this study suggested that major hepatobiliary resection and caudate lobe resection provide R0 resection and improve survival rate for HC. As the caudate lobe is infiltrated by HC either directly due to the close anatomic relationship or by invading the biliary branches, routine caudate lobe resection should be performed for curative treatment of HC. Furthermore, this study also provided readers with important information regarding the HC treatment and variables that increase survival rate..

***Terminology***

HC is an uncommon malignancy with a relatively poor prognosis. HC is the most common type of biliary tract malignancy, arising at the confluence of the right and left hepatic ducts.

***Peer-review***

This is an interesting manuscript with a significant number of patients treating an important topic, and the aim of this study is to determine predictors of long term survival after resection of HC.

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**P-Reviewer:** Cheon YK, Garancini M, Liu XF **S-Editor:** Gong ZM

**L-Editor:** **E-Editor:**

**Table 1 Baseline characteristics *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **< 5-yr survival (*n* = 209)** | **> 5-yr survival (*n* = 34)** | ***P* value** |
| Age | 54.59 ± 4.98 | 50.47 ± 4.45 | 0.001 |
| Sex |  |  |  |
| Male | 124 (59.3) | 23 (67.6) | 0.09 |
| Female | 85 (40.7) | 11 (32.4) |  |
| Symptoms |  |  |  |
| Pain | 73 (34.9) | 12 (35.3) | 0.97 |
| Jaundice  | 206 (98.6) | 34 (100) | 0.95 |
| Weight Loss  | 97 (46.4) | 13 (38.2) | 0.349 |
| Serum Albumin | 3.7 (± 0.46) | 3.82 (± 0.31) | 0.162 |
| Total Serum Bilirubin | 15.29 (± 9.74) | 15.13 (± 9.41) | 0.928 |
| Serum Alkaline Phosphatase | 29.92 (± 41.62) | 38.74 (± 24.12) | 0.231 |
| SGPT | 97.33 (± 112.84) | 89.18 (± 52.74) | 0.680 |
| Ca19-9 | 395.71 ± 31.43 | 254.06 ± 42.19 | <0.0001 |
| HCV | 86 (41.1) | 10 (29.4) | 0.180 |
| Preoperative biliary drainage | 90 (43.06) | 18 (52.9) | 0.38 |
| No preoperative biliary drainage | 119 (66.94) | 16 (47.1) |  |
| ERCP | 25 (11.96) | 9 (26.5) | 0.025 |
| PTD | 65 (31.1) | 9 (26.5) | 0.564 |

HCV: hepatitis C virus; ERCP: endoscopic retrograde cholangiopancreatography; SGPT: serum glutamic-pyruvic transaminase; PTD: preoperative biliary drainage.

**Table 2 operative data *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **< 5-yr survival** | **> 5-yr survival** | ***P* value** |
| Liver status |  |  | 0.02 |
| Cirrhosis (*n* = 102) | 97 (46.41) | 5 (14.7) |  |
| Non cirrhotic (*n* = 141) | 112 (53.58) | 29 (85.29) |  |
| Bismuth corlette classification |  |  | 0.68 |
| Type I, II | 63 (30.14) | 11 (32.35) |  |
| Type III | 146 (69.85) | 23 (67.64) |  |
| Type IV | 0 | 0 |  |
| Extent of hepatic resection |  |  |  |
| Type of resection |  |  | 0.001 |
| Localized resection (*n* = 70) | 66 (31.57) | 4 (11.76) |  |
| Major resection (*n* = 173) | 143 (68.42) | 30 )88.23) |  |
| Types of major resection |  |  | 0.07 |
| Lt hepatectomy (*n* = 102) | 81 (38.75) | 21 (61.76) |  |
| Rt hepatectomy (*n* = 71) | 62 (29.66) | 9 (26.47) |  |
| Segment 1 resection | 79 (37.79) | 23 (67.64) | 0.006 |
| Number of anastomosis |  |  | 0.85 |
| Single | 86 (41.14) | 18 (52.9) |  |
| Multiple | 123 (58.85) | 16 (47.1) |  |
| Blood transfusion |  |  | 0.91 |
| < 3 units | 149 (71.3) | 24 (70.58) |  |
| ≥ 3 units | 60 (28.7) | 10 (29.41) |  |
| Operative time | 4.28 | 4.28 | 0.75 |

**Table 3 Postoperative data *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **< 5-yr survival** | **> 5-yr survival** | ***P* value** |
| Hospital stay | 13 | 11.78 | 0.33 |
| Bile Leakage | 75 (35.88) | 7 (20.0) | 0.08 |
| Wound Infection | 50 (23.9) | 6 (17.6) | 0.39 |
| Early LCF | 38 (18.18) | 1 (2.9) | 0.023 |
| Collection | 38 (18.18) | 6 (17.6) | 0.94 |
| Bleeding and fistula | 13 (6.2) | 1 (2.9) | 0.42 |
| Lymph node metastasis | 81 (41.8) | 6 (17.6) | 0.008 |
| Histological grade |  |  | 0.033 |
| Well differentiated | 78 (37.32) | 20 (58.82) |  |
| Moderately differentiated | 83 (39.71) | 11 (32.35) |  |
| Poorly differentiated | 48 (23.0) | 3 (8.82) |  |
| Safety margin |  |  | < 0.0001 |
| R0 | 93 (44.5%) | 28 (82.35) |  |
| R1 | 116 (55.5) | 6 (17.6) |  |
| Recurrence |  |  | 0.88 |
| Hepatic recurrence | 51 (24.4) | 8 (23.52) |  |
| Local recurrence | 27 (12.9) | 6 (17.64) |  |
| Late LCF | 51 (51.5) | 8 (33.3) | 0.11 |

LCF: liver cell failure.

**Table 4 Multivariate cox regression after resection of hilar cholangiocarcinoma**

| **Variables** | ***P* value** | **Oddis ratio** | **95%CI for Exp (B)** |
| --- | --- | --- | --- |
| **Lower** | **Upper** |
| Liver status | 0.000 | 11.780 | 5.271 | 26.327 |
| Safety margin | 0.000 | 4.937 | 2.251 | 10.826 |
| Type of resection | 0.984 | 1.006 | .564 | 1.795 |
| Caudate lobe resection | 0.000 | 3.808 | 1.878 | 7.725 |
| Lymph node status | 0.000 | .080 | .029 | .217 |
| Tumour differentiation | 0.265 | .819 | .577 | 1.164 |
| Age | 0.055 | 1.040 | .999 | 1.084 |
| Early LCF | 0.367 | 1.415 | .666 | 3.003 |
| CA199 | 0.000 | 1.010 | 1.005 | 1.015 |

A



B



C



D



E



**Figure 1 Actuarial survival (Kaplan Meier analysis) after resection of hilar cholangiocarcinoma: influence of liver status (A), safety margin (B), caudate lobe resection (C), type of resection (D), and lymph node status (E).**