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TITOLO DELLA TESI DI DOTTORATO

RISULTATI E FATTORI PROGNOSTICI DEL COLANGIOCARCINOMA INTRAEPATICO E PERI-ILARE DOPO TRATTAMENTO CHIRURGICO

S.S.D. MED/18

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Abstract

Introduction: Prognosis of perihilar and intrahepatic cholangiocarcinoma is dismal. Curative resection is the only chance of survival. Prognostic factors of survival after surgery, onset and treatment of recurrence and the reports of results during the years is still under debate in literature.

Material and Methods: Prospectively data of 95 patients with perihilar (PCC) and 84 with intrahepatic cholangiocarcinoma (ICC) submitted to surgical resection in Division of General Surgery of the University of Verona Medical School between September 1990 and September 2012 were evaluate.

Results: for PCC patients, Preoperative serum level of Ca 19.9 and CEA, major hepatectomy, caudate lobe resection, portal vein resection and reconstruction, and lymph node dissection, absence of satellite nodules, N0 status and lower TMN stage resulted as prognostic factors for longer survival at univariate analisys. The multivariate analysis confirmed the serum value of Ca 19.9 lower than 500 U/L, and the absebnce of positive lymphnodal involvement as factor strongly related to survival. Median follow up was of 29 months (range 4-107). Median overall survival was 28.8 months; cumulative proportion survival at 3 and 5 years were 43.2% and 23.9% respectively. For ICC patients, at univariate analysis, the CEA > 5 ng/dL, the presence of lymph node metastases, macroscopic vascular invasion, the presence of intrahepatic metastases, an higher grade of differentiation, an higher TNM stage and positive resection margins (R +) were significantly related to survival. Cox's regression multivariate model identified the high serum value of CEA, the presence of intrahepatic metastases and the radicality as being significantly related to survival with hazard ratios (HR) of 9.8, 2.2 and 2.3 , respectively. The overall median survival time was 31.8 months, with 3- and 5-year actuarial survival rates of 44.5% and 26.8%, respectively. For all patients, the 1- and 5-year disease-free survival was 69.4% and 21.1%. In patients with PCC, recurrences were more frequently extrahepatic (71%). High lymph-node ratio, multifocality, portal resection/reconstruction, perineural invasion and elevated serum level of CEA were significantly associated with recurrence. Nine (19.1%) patients were submitted to surgery, 29 patients were submitted to chemo or radiotherapy (61.8%), 9 patients (19.1%) received best supportive care. In patients affected by ICC recurrences occurred more frequently into the liver (52%). High level of Ca 19.9, a tumor size higher than 30 mm, R1 resection, multifocality and histological grading are factors correlated to recurrence. Six (19.6%) patients underwent surgical resection of recurrence, chemotherapy was performed in 14 patients (45.2%) and the remnant 11 patients received best supportive care. When recurrence was surgically treated patients showed a longer survival after recurrence than patients submitted to chemo or radiotherapy (1- and 3-year survival of 64.8% and 25.9% vs. 60.3% and 18.8% respectively, p=0.005). Among patients affected by PCC, 29 were submitted before 2005 and 55 after 2005. The 5-year overall survival was significantly increased before and after 2005 (12.5% and 39.4%, respectively, p=0.01). In patients submitted to surgery after 2005 respect than in those treated before 2005, it is shown a lower recurrence rate (51.7% vs. 78.9%, p=0.07) and a higher 3-year disease-free survival (49.6% vs. 26.3%, respectively, p=0.01). Remarkably, in patients submitted to surgery after 2005 with radical resection and with no positive lymph-nodes metastases, the 5-year survival was 73.8%, compared to 13.6% of the same patients submitted to surgery before 2005. In patients affected by ICC, 25 were submitted to surgery before and 58 after 1st January, 2005. Patients were older after 2005. Tumor seemed to be more advanced after 2005: indeed, the tumors were bigger in size and with more macrovascular involvement rate in patients

submitted to surgery after 2005 than in patients submitted before 2005. So, the surgery resulted more aggressive after 2005, with more major hepatectomy and more lymph node harvested than before, even if with no difference in complication rate between the two periods. R0 resections were more performed after 2005 than before. Nevertheless, these results did not allow a survival gain in patients before and after 2005 (p=0.48).

Conclusions: in patients with PCC we demonstrated that an low preoperative serum level of Ca 19.9 and CEA, major hepatectomy, caudate lobe resection, portal vein resection and reconstruction, and large lymph node dissection with more than 10 lymph nodes were positive prognostic factors for longer survival. Besides, perioperative and surgical thecniques for the treatment of PCC has been evolved during the years. In our institution, patients treated for PCC in the last 10 years gained a significantly better overall survival rates compared to patients treated before, especially if radical resections were performed with no lymph node involved. Regarding patients with ICC, CEA > 5 ng/dL, the presence of lymph node metastases, macroscopic vascular invasion, the presence of intrahepatic metastases, an higher grade of differentiation, an higher TNM stage and positive resection margins (R +) were significantly related to survival. MF type demonstrated to have better prognosis than other types of ICC. Recurrence is confirmed to be a major prognostic factor. When feasible, aggressive surgical resection of recurrence can improve the prognosis in these patients, especially in patients with ICC. In patients with PCC, in which recurrence is more often unresectable, aggressive adjuvant treatment protocol could improve survival reducing the frequency of recurrences.

Abstract

Introduzione: La prognosi del colangiocarcinoma peri-ilare ed intraepatico è scarsa. La resezione radicale è l'unico possibilità di sopravvivenza in questi pazienti. Tuttavia,i fattori prognostici di sopravvivenza dopo la resezione, l'insorgenza e il trattamento della recidiva e I miglioramenti nel tempo del trattamento di questi tumori sono ancora oggetto di dibattito in letteratura.

Materiali e Metodi: Sono stati prospetticamente analizzati i dati di 95 pazienti affetti da colangiocarcinoma peri-ilare (PCC) ed 84 affetti da intraepatico (ICC), sottoposti a resezione epatica nella Divisione di Chirurgia Generale dell'Università di Verona tra il settembre 1990 e il settembre 2012.

Risultati: Riguardo i pazienti affetti da PCC i livelli sierici preoperatori di Ca 19.9 e CEA, l'esecuzione di una epatectomia maggiore, la resezione del lobo caudato, la resezione e la ricostruzione portale, l'estesa dissezione linfonodale, l'assenza di noduli satelliti, lo stato N0 e un basso grado secondo TNM stage sono fattori prognosticamente positivi per la sopravvivenza. L'analisi multivariata ha confermato che un basso valore di Ca 19.9 e l'assenza di coinvolgimento linfonodale fattori fortemente correlati con la sopravvivenza. La sopravvivenza mediana è stata di 28.8 mesi, la sopravvivenza a 3 e 5 anni è risultata del 43.2% e 23.9%. Nei pazienti ICC, all'analisi univariata, il CEA> 5 ng / dL, la presenza di metastasi linfonodali, l'invasione vascolare macroscopica, la presenza di metastasi intraepatiche, un più alto grado di differenziazione, uno stadio TNM superiore e margini di resezione positivi (R +) erano significativamente correlate alla sopravvivenza. L'analisi multivariata ha identificato l'alto valore sierico del CEA, la presenza di metastasi intraepatiche e la radicalità come significativamente correlata alla sopravvivenza con HR di 9.8, 2.2 e 2.3, rispettivamente. La sopravvivenza mediana è stata di 31.8 months, con una sopravvivenza a 3 e 5 anni del 44.5% e 26.8%. Globalmente, la sopravvivenza libera da malattia a 1 e 5 anni è stata del 69.4% e del 21.1%. Nei pazienti affetti da PCC, le sede di recidiva è stata più frequentemente extraepatica (71%). La multifocalità, la resezione / ricostruzione portale, l'invasione perineurale ed elevati livelli sierici di CEA sono risultati significativamente associati alla recidiva. Nove (19,1%) pazienti sono stati sottoposti a intervento chirurgico, 29 pazienti sono stati sottoposti a chemio o radioterapia (61,8%), 9 pazienti (19,1%) hanno ricevuto terapia di supporto. Nei pazienti affetti da ICC la sede direcidiva si è verificata più frequentemente nel fegato (52%). Un alto livello di Ca 19.9, una dimensione del tumore superiore a 30 mm, una resezione R1, la multifocalità e un grading istologico sono risultati fattori correlati alla recidiva. Sei (19.6%) pazienti sono stati sottoposti a resezione chirurgica come terapia della recidiva, la chemioterapia è stata eseguita in 14 pazienti (45,2%) e le rimanenti 11 pazienti hanno ricevuto terapia di supporto. Quando la recidiva è trattata chirurgicamente i pazienti hanno mostrato una sopravvivenza più lunga dopo la recidiva rispetto ai pazienti sottoposti a chemio o radioterapia, con una sopravvivenza a1 e 3 anni del 64,8% e del 25,9% contro il 60,3% e il 18,8%, rispettivamente, p = 0,005.
Tra i pazienti affetti da PCC, 29 sono stati sottoposti all'intervento prima del 2005 e 55 dopo il 2005. La sopravvivenza globale a 5 anni è risultato significativamente aumentata dopo il 2005 (12,5% prima del 2005 e 39,4% dopo il 2005, p = 0,01). In pazienti sottoposti a intervento chirurgico dopo il 2005 rispetto a quelli trattati prima del 2005, si è mostrato un tasso più basso di recidiva (51,7% vs 78,9%, p = 0,07) e una sopravvivenza libera da malattia a 3 anni più alta (49,6% vs. 26,3 % rispettivamente, p = 0,01).

Sorprendentemente, in pazienti sottoposti a intervento chirurgico dopo il 2005 con resezione radicale e senza metastasi linfonodali, la sopravvivenza a 5 anni è stata del 73,8%, rispetto al 13,6% degli stessi pazienti sottoposti a intervento chirurgico prima del 2005. Nei pazienti affetti da ICC, 25 sono stati sottoposti a chirurgia prima e 58 dopo il 1 ° gennaio 2005. I pazienti avevano un'età più elevata dopo il 2005. Lo stadio tumorale è risultato essere più avanzato dopo il 2005: infatti, i tumori erano di dimensioni maggiori e con maggiore coinvolgimento macrovascolare in pazienti sottoposti a intervento chirurgico dopo il 2005 rispetto ai pazienti sottoposti prima del 2005. Dopo il 2005 sono state eseguite un maggior numero di epatectomie maggiori e più ampie dissezioni linfonodali, anche se i tassi di complicanze non hanno dimostrato differenze. Le resezioni radicali sono state più eseguite in maggior numero dopo il 2005 rispetto a prima. Tuttavia, questi risultati non hanno permesso un guadagno di sopravvivenza in pazienti prima e dopo il 2005 ($p = 0,48$).

Conclusioni: nei pazienti con PCC un basso livello sierico preoperatorio di Ca 19.9 e CEA, l'esecuzione di una epatectomia maggiore, la resezione del lobo caudato, la resezione e ricostruzione della vena porta, e un'ampia dissezione linfonodale sono risultati fattori prognostici positivi per la sopravvivenza. Nel nostro istituto, i pazienti trattati per PCC negli ultimi 10 anni ha ottenuto un significativo miglioramento dei tassi di sopravvivenza globale rispetto ai pazienti trattati in precedenza, soprattutto se sono stati eseguite resezioni radicali senza linfonodi coinvolti. Per quanto riguarda i pazienti con ICC, CEA> 5 ng / dL, la presenza di metastasi linfonodali, l'invasione vascolare macroscopica, la presenza di metastasi intraepatiche, un più alto grado di differenziazione, uno stadio TNM superiore e margini di resezione positivi (R +) erano significativamente correlate alla sopravvivenza. Il tipo MF ha dimostrato di avere una migliore prognosi rispetto ad altri tipi di ICC. La recidiva si conferma essere un importante fattore prognostico. Quando possibile, la resezione chirurgica aggressiva di recidiva può migliorare la prognosi in questi pazienti, soprattutto nei pazienti con ICC. Nei pazienti con PCC, in cui ricorrenza è più spesso resecabile, protocollo di trattamento adiuvante aggressivo potrebbe migliorare la sopravvivenza ridurre la frequenza delle recidive.

Introduction

Cholangiocarcinoma is a malignant transformation of bile duct epithelium; it represents proximally 10% of all primary hepatobiliary cancer [1, 2] . This tumor is the second most frequent primary liver tumor and its incidence is increasing in Western countries [3]. Cholangiocarcinoma is classified as intrahepatic (ICC), perihilar (PCC) and distal type, according to its origin from proximal intrahepatic bile ducts (ICC), from the epithelium of the right or left hepatic ducts at biliary confluence (PCC) or from distal part of common bile duct [1, 4].

Perihilar cholangiocarcinoma (PCC), also called Klatskin tumor [5], represent approximately two third of all cases of bile ducts tumors [4] . It was defined as tumor involving biliary confluence, however there are still some difficult in preoperative definition and proper histological classification [6] [7].

Different clinicopathological factors have been previously evaluated and related to survival: radical resection, vascular invasion, perineural invasion, tumor size, multifocality, lymph node metastasis, tumor stage, tumor grading and positive resection margins [8-10].

Surgical radical resection (R0) and transplantation in selected cases are still the only therapeutic option to achieve longer survival [11-13] , however prognosis is dismal and rarely 5 years survival exceed 30% [14] .

Staging systems give information about prognosis, stratification of patients according to tumor stage, guide for different type of therapy and allowed to compare different treatments among different institutions over the time [15]. For these reasons, as for others tumors, also for perihilar cholangiocarcinoma were created different staging systems.

Prognostic factors of PCC

The local extension is a main prognostic factors The 7^{th} TNM classification consider the early stage (T1) tumor for the extrahepatic bile duct cancers as tumor confined to the bile duct wall. On imaging this tumor presents as wall thickening of the bile duct. The low (fat) attenuation of the periductal fat is preserved. The T2 tumors are cancers that invade the periductal fat (T2a) or the liver (T2b). The proximal extrahepatic bile duct tumors may extend to the portal vein or hepatic artery. The unilateral vascular extension is considered T3, whereas more advanced extension is considered T4. The latter (T4) includes extension into the main portal vein, common hepatic artery, contralateral vascular extension, and involvement of secondary biliary radical. Hepatic parenchymal involvement is now classified as T2[16].

Also lymph/nodal metastases are an important prognostic factor. Lymph/nodal involvement are present in 30/50% of patients submitted to surgical treatment. They are related to the T-stage indeed, in T1 staged

tumor are noticed in 16% of cases, in T2 staged tumor in 28% of cases, in T3 in 40% and in T4 staged tumor in 60%. In patients with no lymph nodal involvement, 5 years survival are reported to be 45%, by contrast, in patients with lymph nodal metastases are 15% [17, 18].

The most common site of distant metastases are liver, the peritoneum, the lung or the bone. Median survival of patients with distant mestastases from PCC is lower than 11 months. They are diagnosed in 30% of patients during the preoperative evaluation or at laparotomy. [19].

Among the macro and microscopical biological pattern, those that modify the prognosis of PCC are the follows: the cellular differentiation, the perineural infiltration, the lymphatic and microvascular involvement. The cellular differentiation is an important prognostic factor: it is shown that the grades G1 and G2 determines an median survival of 35/40 months, whereas in the grade G3 it is about 15/20 months[20].

Acconding to some studies, the perineural infiltration is present in the 60% of cases, the 5 year survival of patients with perineural infiltration is significantly lower than in patients without it (30% vs. 68%)[17].

Lymphatic involvement is described in more than 70% of cases, in these patients the 5 year survival is about 30%, compared to 48% in patients without lympatic involvement[17].

Microvascular involvement is also importanto to determine the prognosis: the 5 year survival in patints withuot and with microvascular uinvolvemt is 40% and 15% respectively[21].

Other biological pattern are nowadays not analyzed in literature in patients with PCC, such as the k ras, p27 or TGβ mutations. Nevertheless, p53 mutations are described among the 38% and 66% of cases and they are related to lower differentation, advanced stage of tumor and nodal involvement[22].

Intrahepatic cholangiocarcinoma arises from intrahepatic bile ducts beyond second order biliary tree[1].

Three macroscopic modality of growth are described in 1997 accordino the Liver Cancer Study Group of Japan (LCSGJ), mass forming (MF), periductal infiltrating (PI), intraductal growing (IG, fig.1). The MF type have nodular growth and well-defined border with liver parenchima, the IP type arises with an infiltrative pattern without a well defined mass, the IG type presents papillar pattern of growth inside the bile ducts. The mixed forms are classified describing the different macroscopical type are most represented (e.g. MF+PI type)[23].

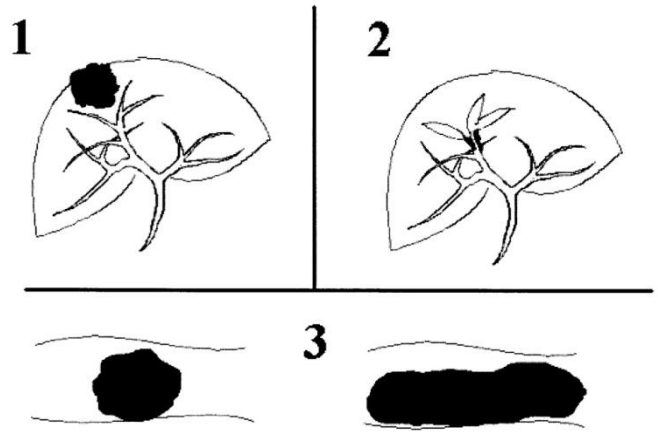


Fig. 1. The three principal pattern of growth of ICC: 1 mass forming; 2 periductal infiltrating; 3 intraductal growing.

The pattern of growth of ICC (MF, PI, IG) involves different biological aggressiveness and neoplastic spread. The MF type are the most frequent (60-70% of cases)[24]; it is shown to have an early portal involvement in the 45% of cases, satellite nodules are presenti in the 36% of cases41-43. The lymph-node involvement is present in about 30% of patients44. the reperted 5-year survival varies from 25% to 48%. The IG pattern of growth is described in 8-23% of resected specimen. It appeares as papillar growth and it is well differentiated in the most of cases. Its vascular, perineural and lymphnodoal involvement rate is generally low. The long term survival after surgical resecton is good, with a 5 year survival between 41% and 80%. The prognosis in these patients is significantly longer compared to patientas with MF and PI types, even with lymph nodal metastases[25].

The PI type demonstates the worst prognosis than the othe two types. Its frequency is about 15-35% of cases and iti is associated with biliary, vascular and lymphatic infiltration. The 5 year overall survival in this patiets varies from 0 to 49%[26].

The mixed form MF+PI is showed in the 25-45% of patients. This type has worse prognosis because its advanced stage at diagnosis and its higher lymphnodal, vascular and intrahepatic metastases rate. The long term survival is low, with a 5 year survival of 10%[26].The site of tumor is significantly related to the pattern of growth: the most tumor in peripherally site is MF type, whereas PI is often centrally sited[27].

The local spread is related to size, multifocality, valscolar and main bile duct involvement. Size is an important prognostic factor: the 5 year survival in patients with tumor less 3 cm in size is about 42%, whereas in patients with tumor more than 6% in size decreases to 0%.

The satellite nodules are described in 20-30% of patients. The 5 year survival in patients with multufocality is reperted to be between 7 and 0% %[26].

Portal involvement is another important prognostic factor, indeed the survival is significantly higher in patients without portal involvement compared to patients with macroscopical portal spread. They present a 3-year survival of 46% and 0% respectively[28].

In literature, the presence of lymph nodal metastases varies from 7 to 73%, with a 5 year survival of 0-17%. The lymph nodal involvement rate is significantly lower in the IG type tumor, while in the mixed form (MF+PI) is significantly higher: according to some Authors, it is about the 20% in former, and in the 80% in the latter. The lymph nodal involvement is related to the tumor stage (some Author reported in 80% of patients with tumor in T4 stage.) and to tumor site, with higher rate in the centrally site tumor (up to 75%) compared to peripherally site tumor (about 45%) [27].

The main biological factors related to prognosis are: the cellular differentiation, the vascular, lymphatic and perineural involvement.

With regards of cellular differentiation, the tumors with well or moderate differentiation present a better prognosis compared to the tumor with low differentiation, with a 5-year survival of 50%, 39% e 0% respectively[29].

The lymphatic involvement is a negative prognostic factor for survival in the literature, none of the patients with lymphatic involvement is shown to survive over 3 years, while a 5-year survival of 70% in patients without lymphatic invasion is reported [30].

According to some studies, patients with perineural invasion have a 5-year survival less than 10%, while it exceeds 60% in patients without this involvement. Moreover, perineural invasion is associated with a high frequency of lymph node metastases and the presence of vascular invasion [30].

Many other biological and molecular prognostic factors were identified. Reduced expression of IL-6 and p27kip1, mutations of K-ras, p53, E-cadherin, α-catenin and β-catenin are associated with advanced cancer, poorly differentiated and with rapid progression[31].

For the preoperative evaluation of operability, sevaral factors must be taken into account: the physical state of the patient and liver function, the volume of the liver remnant (Future Liver Remnant, FLR), the extension of the biliary tumor, the vascular involvement, the presence of lobe atrophy, lymph node involvement, the presence of distant metastases[32].

The clinical factors that most affect the outcome of the surgery are the preoperative jaundice and the consequently need of drainage and the volume of the residual liver of the patient.

There are two schools of thought on preoperative biliary drainage in jaundiced patients who are candidates for major hepatectomy for hilar cholangiocarcinoma. The former [1, 33] school does not routinely use preoperative drainage before hepatic resection but uses it only in a subgroup of malnourished patients with hypoalbuminemia, cholangitis, or long standing (>4 weeks) jaundice, because it believes that the theoretical advantages of preoperative drainage decrease with a greater likelihood of complications (choleperitoneum, cholangitis, bleeding) and seeding along the tract of the drain, which can compromise recovery. The latter school[21, 34], to whom some European groups ascribe [35], routinely uses a single or multiple percutaneous transhepatic biliary drainages. However, probably these differences reflect a different way to approach this type of tumor: less aggressive in the Euro-American group and more aggressive in the Asian group. Today, nasobiliary drainage has a more significant role and is employed more often, and it presents the lowest rate of complications among the different drainage procedures[36, 37]. Unilateral drainage of the FLR is sufficient in the majority of patients. However, unilateral or bilateral drainage should be determined on a case-by-case basis, considering the operative procedure, liver function, and/or the presence or absence of cholangitis. The preferred type of biliary drainage should be endoscopic, with the use of selective nasobiliary drainage. In Bismuth-Corlette tumors, type III and particularly in type IV endoscopic approach with nasobiliary drainage showed lower efficacy because multiple drainages or percutaneous transhepatic biliary drainage are often required to drain excluded biliary segments or to treat cholangitis. In all cases with external biliary drainage, reinfusion of bile is strongly suggested[36, 37].

The curative treatment of cholangiocarcinoma frequently requires major liver resections, which can lead to a reduction of liver function with risk of postoperative liver failure [38]. The preoperative portal vein embolization (PVE) determines the atrophy of the embolized lobe and stimulates hypertrophy of the residue liver. This procedure can be performed in experienced centers with a high success rate (80% of cases) and with complications in only 6-15% of cases. The minimum volume liver remnant (FLR) should be about 25-30% [38]. A correlation between remnant volume and postoperative complications has been demonstrated in the literature. Abdalla showed an incidence of 50% of complications in patients with a FLR less than 20% and 13% in patients with a FLR more than 20% 125 . In patients with liver disease or jaundice the postoperative remnant volume must be at least 40% to reduce the incidence of complications[39].

Patients with PCC present operability between 20% and 60%. In 25%-46% of patients unresectability is confirmed only after laparotomy [40].

The radical surgical resection (R0) is the treatment of choice and the only that can obtain an adequate long-term survival. To obtain R0 resections are used: resection of the bile duct and biliary-digestive anastomosis;

hepatic resection; resection of the caudate lobe (S1); vascular resection (portal and / or hepatic artery); resection of the pancreatic head and duodenum (HPD).

The criteria for resectability are highly variable in the experiences reported in the literature; following the classification of the MSKCC are excluded from the surgical treatment the patients: with involvement of the biliary tree above the branches of second order bilaterally, with atrophy of a liver lobe contralateral, with infiltration of the contralateral biliary branches of second order or portal branch, with infiltration of the common trunk of the portal vein or hepatic artery, with para-aortic, celiac, retropancreatic lymph node involvement [41].

Isolated resection of extrahepatic bile duct is indicated only for the treatment of neoplasia type I and II according to the Bismuth-Corlette classification. [41]. However, a number of criticisms have been leveled against this indication and this procedure should be considered ineffective, with regard to the long-term results. In the case series reported by MSKCC there were no 5-year survival in patients who had undergone resection biliary isolated[19]. Similar results were reported by Miyazaki and Nimura: in a study of 100 patients who had undergone this surgery, mortality occurred for all within 65 months. Moreover, this type of surgery has a high rate of recurrence, greater than 76%. The association of liver resection of the common bile allows better survival rate [42].

The resection of caudate lobe (S1) is always indicated in association with the hepatectomy for the high frequency of infiltration of the bile dute to the caudate lobe (between 48% and 96%)[43]. The need of resection of the caudate lobe has been described for the first time in 1990 by Nimura [44] and is now widely accepted. Afterwards Sugiura showed a 5-year survival of 46% for patients undergoing liver resection combined with resection of the caudate lobe, compared with 12% for those without resection of the caudate lobe [45].

The results after surgical resection of PCC is still burdened by a high incidence of serious complications in about 50% of patients and perioperative mortality between 5% and 18% of cases [46]. Several factors are related with the postoperative morbidity: jaundice, malnutrition, the extent of liver resection and type of surgery. The postoperative liver failure is correlated with the volume of the liver remnant: the rate of organ failure is 16% in patients with liver resection less than 50% of the total volume, but increases to 38% in patients with resection over 50% [47]. Other frequent postoperative complications are: biliary leakage, infectious complications and intra-abdominal bleeding. The incidence in the literature varies between 1% and 22% of cases[47]. The mortality reported in the literature varies between 2% and 10% [48, 49], and decreases to 0% in some recent experiences [46]. The invasion of the portal vein is generally associated

with homolateral lobar atrophy, but it is not a contraindication to resection[50]. However, contraindications to resection is related to the extent of portal involvement: in cases of obstruction or involvement of the main portal trunk; in cases of bilateral portal involvement. Portal resection is a negative prognostic factor. However, this intervention improves survival in patients with portal involvement: in patients with liver resection combined with portal resection compared to patients who had undergone only liver resection the 3 and 5 years survivals were 26 and 10% and 54 and 37%, respectively[51]. In recent experiences in literature, resection portal does not increase perioperative complications and mortality[51]. Literature on the resection and reconstruction of hepatic artery is still poor, because of the reconstruction of the hepatic artery is performed less frequently than that of the portal vein. This is due to the fact that, often, this condition is associated with a very advanced stage of disease. According to some authors[19], the involvement of the hepatic artery is a contraindication to surgical resection. Although recent studies the reconstruction of the hepatic artery associated to liver resection show a lower mortality (0-8%)[51], this procedure is burdened by higher rates of mortality and morbidity compared to hepatectomy without vascular reconstruction. Miyazaki observed a mortality rate of 78% in the group of patients who underwent reconstruction of the hepatic artery compared with 38% in patients with portal vein resection and 36% in patients without vascular resection[51]. For this reason, currently the reconstruction of the hepatic artery associated with hepatectomy is performed only if allows a radical resection of an advanced cancer. Nagoya University group revealed that the only absolute contraindication to resection-arterial reconstruction is bilaterally involvement of hepatic artery by the tumor [42, 52]. In some cases with neoplastic infiltration of the distal bile duct, in order to achieve the radical surgery, a liver resection can be associated with duodenal and pancreatic head resection (HPD) [52]. This procedure increases the rate of surgical complications: Sano observed postoperative complications in more than 85% of patients with HPD[46]. Nagino reported an incidence of liver failure of 50% in patients with HPD combined compared to 25% in patients with liver resection alone [32]. Survival after resection has improved in recent years, with a 5 years survival rate from 12% to 40%. Neuhaus showed a 5-year survival in R0 resections of 39% compared with 9%, and 0% for R1 and R2 resections[17].

Operability in patients with intrahepatic cholangiocarcinoma is reported to be between 20% and 70% [53, 54], for the presence of intrahepatic metastasis or distant, vascular invasion or peritoneal carcinomatosis. The radical surgical resection (R0) is the treatment of choice and the only one that allows to obtain an adequate long-term survival. To achieve the radical surgery a major hepatectomy may be needed; furthermore, it may be required resection of the extrahepatic bile duct, hilar vascular structures, vena cava and diaphragm [53].Normally, the ICC onsets in non injuried liver, therefore major resections can be

performed with low morbidity and mortality. The complication rate is related to the type of resection and varies between 35% and 55% [26, 53]. In most of the studies reported a mortality rate of less than 5%, often linked to major liver resections or associated with vascular and biliary resection [52]. In literature, the 5-year survival varies from 14% to 36% and never exceeds 40%, even in the most recent analyzes. The radical surgical resection (R0) is the only factor that can afford satisfactory long-term survivals, up to 80%. The non-radical resection (R1), however, allows a 5-year survival between 0% and 25%[26, 53].

Recurrence of the disease is common even after R0 resection (46%-68%) [50]. It frequently occurs early (within 2 years) and it is usually the cause of death of patients [8] [46]. The factors related to recurrence are well-known in literature. However, the locations of recurrence and which treatment, either surgical or chemotherapic or supportive care, allows the better survival after recurrence, has not yet been clearly established.

In patient with intrahepatic cholangiocarcinoma (ICC), the most important factors related to recurrence described are the tumor size more than 45 mm, the portal involvement, the presence of lymph nodal metastases and a high preoperative value of serum Ca 19.-9 [55].

In patients with peri-hilar cholangiocarcinoma (PCC), the median disease-free survival reported in the literature is 19 months [8]. The prognostic factor related to the onset of recurrence are the presence and the length of margin involved by biliary tumor, the presence of lymph node metastasis and the tumor grading.

The treatment varies according to the location and extension of recurrence; in most cases it is only palliative. Nevertheless, it has been reported that the surgical treatment, including the transplant, showed good results of long term survival in very selected cases [56].

Material and methods

Patients and data collection

Patients submitted to surgical resection for cholangiocarcinoma in Division of General Surgery of the University of Verona Medical School between September 1990 and September 2012 were evaluate for this study. Data were collected retrospectively in 2006 and after that prospectively. From database patients with perihilar cholangiocarcinoma (PCC) who underwent surgical resection were analyzed. All patients included in the study underwent surgical resection with curative intent. Patients who deceased in perioperative period (within 30 days after surgery) were excluded from analysis.

All patients signed informed consent before surgery.

Preoperative evaluation

The preoperative evaluation included blood chemistry tests with a complete blood count, PT, aPTT, direct and total bilirubin, albumin, AST, ALT, ALP, GGT, CEA, CA19.9, alpha-fetoprotein and serology for hepatitis viruses (HBV, HCV). The tumor extent was evaluated with ultrasonography, color Doppler ultrasonography and CT or MRI. The differential diagnosis between cholangiocarcinoma and gastro-intestinal tumor liver metastases was made with tumor histology or by the exclusion of other primary tumors by esophagogastroduodenoscopy and colonoscopy.

In patients with obstructive jaundice, the extent of the tumor was assessed using different diagnostic methods during the study period. Between 1990 and 1997, all of the patients underwent percutaneous trans-hepatic cholangiography (PTC) with the placement of single or multiple biliary drains. Subsequently, non-invasive diagnostic methods, such as colangio-pancreatography MRI, were primarily used. All patients with obstructive jaundice (a serum bilirubin level greater than 3 mg/dL) underwent percutaneous biliary drainage to more precisely define the longitudinal extension of the tumor and to reduce the serum bilirubin to less than 3 mg/dL. A percutaneous trahepatic biliary drainage (PTBD) was preferentially positioned only in the future remnant liver. In patients with segmental cholangitis, multiple hepatic drainages of the excluded biliary segments were performed [57] . More recently, endoscopic biliary drainage, CT-PET and diagnostic laparoscopy was introduced in selected patients.

Surgical technique

During surgery, intraoperative ultrasonography was routinely used to confirm the preoperative diagnosis, to evaluate the relationship between the tumor and blood vessels and to evaluate the presence of intrahepatic metastases. The extent of liver resection was defined according to the Brisbane classification [58] . Common bile duct resection was performed in all cases because of macroscopic involvement by the tumor. In cases of

bile duct resection, frozen sections of the bile duct were made intraoperatively.

Lymphadenectomy of the regional LN was classified according to the Japanese Society of Biliary Surgery (JSBS) classification [59]. The LNs of the hepatoduodenal ligament (12 h, 12a, 12p, 12b), the proper hepatic artery (8) and the posterior surface of the pancreatic head (13) were harvested. The paraaortic LNs (16) and the LNs of other stations were retrieved if they were macroscopically suspected for metastases. The surgical LN dissection technique includes the complete dissection of the hilar structures; all fatty tissue of the hepatoduodenal ligament was retrieved and sent to pathologist.

Pathological evaluation

Tumors classification depended on the location of the main tumor and on the presence of histologically proven invasion of the main bile ducts. Tumors with involvement of the hepatic hilus structures requiring resection of the biliary confluence associated with the liver and caudate lobe resection in some cases were defined as peri-hilar cholangiocarcinoma [6, 60, 61].

The microscopic direct invasion of the bile duct wall, the portal pedicle and neural tissue was verified in all surgical specimens; all fatty tissue surrounding the vessels of the hepatoduodenal ligament and from others lymph node stations were analyzed. Metastatic LNs were defined as N+. Invasion of the wall of the major portal or hepatic vein branches and confirmed by the pathological examination was defined as macroscopic vascular invasion. Failed radical resection (R1) was defined as the presence of microscopic disease at resection margins of the specimen (bile ducts and liver).

Postoperative course

Complications were classified according to the Zurich Classification [62]. Complications greater than grade 3a were classified as major. When more than one complication occurred, the higher grade was reported.

Mortality, complication grade 5, was considered as peri-operative mortality if it occurred within 30 days of surgery and it was one of exclusion criteria.

Postoperative treatment and follow up

After surgery, the patients were regularly followed up with blood tests, tumor markers (CEA, CA19.9) and abdominal CT or MRI every 6 months. In cases of suspected recurrence at radiological exams, PET-CT was performed. Occurrence of disease recurrence, time of recurrence, decease and time of death were recorded.

Statistical Analysis

The differences between categorical and continue variables were analyzed with a chi-square, Fisher's exact, t-student and Mann–Whitney U tests as appropriated. Overall survival (OS) was defined as the time interval between treatment and death from any cause. Time was censored at the date of last follow-up assessment for patients who were still alive. Survival curves were estimated using the Kaplan-Meier method with the Log Rank test to verify significance of differences. Variables statistically significant at univariate analysis were investigated in the Cox model and by testing (using a likelihood-ratio test) whether the coefficient of the interaction term was significantly different from zero. A p-value lower then 0.05 was considered statistically significant.

Results

From September 1990 to September 2012, 211 patients underwent surgery for PCC and ICC. After abdominal exploration, 32 patients (19 with PCC and 13 with ICC) were excluded from surgical resection because of the presence of peritoneal carcinomatosis, extensive vascular involvement, or multiple bilateral intrahepatic metastases.

Patients with peri-hilar cholangiocarcinoma

Ninety-five patients were classified as PCC. Eleven patients were submitted to R2 resections, thus were excluded from analysis. Clinical characteristics of the remnant 84 patients are summarised in table 1. Twenty-four patients were female (28.6%) and 60 male (71.4). Median age was 68 (range 30-83). Majority of patients were symptomatic (81%) at time of diagnosis and symptom most frequent was jaundice (70.2%); 48 patients (57.1%) underwent positioning of biliary drainage. Preoperative median value of CA 19.9 was 92 U/mL with range between 3.5 U/mL and 10486 U/mL. Three patients were submitted to preoperative portal vein embolization because of small remnant liver volume.

Table 1: Clinical characteristics of patients with PCC

		Nr. Cases (84)	**Percentage**
Gender	Female	24	28.6
	Male	60	71.4
Age	Median; range	68; 30 - 83	
Symptoms	Present	68	81
	Absent	16	19
Jaundice	Present	59	70.2
	Absent	25	29.8
Preoperative biliary drainage	Positioned	48	57.1
	Not positioned	36	42.9
Liver status	Normal	65	77.4
	Pathological*	13	22.6
CEA (ng/dL)	Median; range	2.0; 0. - 35	
CA 19.9 (U/mL)	Median; range	92; 3.5 - 10486	
Preoperative portal vein embolization	Performed	3	3.6
	Not performed	81	96.4
Neoadiuvant chemotherapy	Performed	6	7.2
	Not performed	78	92.8

* Liver status pathological: cirrhosis, fibrosis, steatosis.

Surgical variables are summarized in table 2. Minor liver resections associated to CBD resection were performed in 5 patients; majority of patients were submitted to major liver resection. Caudate lobe resection was performed in 66 (78.6%) of patients and lymph node dissection in 80 (95.2%) of patients. Resection and reconstruction of hepatic vein or hepatic artery due to vascular infiltration by tumor were performed in 17 and 4 cases respectively. Median operation time was 547 minutes (range 250-780).Median postoperative length of stay was 20 days with range between 7 and 213 days. Postoperative complications occurred in 38 patients (45.2%). Complications equal to or greater than grade 3a, excluding grade 5, occurred in 6 (7.1%) patients. Perioperative mortality was 2.4% (2 patients).

Table 2: Surgical characteristics of patients with PCC.

		Nr. Cases (84)	**Percentage**
Operation type	Bile duct resection only	11	13.1
	Segmentect- / Bisegmentectomy	6	7.1
	Right hepatectomy	22	26.2
	Right trisectionectomy	8	9.5
	Left hepatectomy	32	38.1
	Left trisectionectomy	5	6
Liver resection	Associated to CBD resection	73	86.9
	Not performed	11	13.1
Hepatectomy	Minor	5	6.8
	Major	68	93.2
Caudate lobe resection	Performed	66	78.6
	Not performed	18	21.4
Vascular clamping	Without clamping	45	54.6
	Pringle maneuver	28	33.4
	Selective clamping	11	13.1
Lymph node dissection	Performed	80	95.2
	Not performed	4	4.8
Portal vein resection	Performed	17	20.2
	Not performed	56	79.8
Hepatic artery resection	Performed	4	4.8
	Not performed	79	95.2
Operative time (minutes)	Median; range	547; 250 - 780	
Postoperative hospital stay (days)	Median; range	20; 7-213	
Postoperative complications	Occurred	38	45.2
	Not occurred	46	54.8

Pathological data are reported in table 3. Radical resection was obtained in 82 patients. Median tumor diameter was of 3 cm (range 2-12); tumor grading was G1 and G2 in 18 and 47 cases and G3 and G4 in 15 and 4 case, respectively. Satellites tumor nodules were present in 10 cases. Macroscopic vascular invasion of major brunch of portal vein or hepatic artery or common portal vein or hepatic artery were present in 49 cases (58.3%). Perineural infiltration was present majority of patients (82.2%). Median number of harvested lymph node was 7 (range 1-27); lymph nodes were positive in 44 patients (52.4%) and median number of positive lymph node was 3 (1-10); Pathological tumor classification according to UICC/AJCC TNM 7th Edition were stage as I, IIA and IIB in 32 cases (46.4%) and III and IV in 37 (53.6%) of cases. Patients were classified according to TNM 7th Edition as stage I and II in 37 cases (44%), in stage IIIA or IIIB in 38 cases (45.2%) and in stage IVA or IVB in 17 cases (20.2%), respectively.

Table 3: Pathological characteristics of patients with PCC

		Nr. Cases (84)	Percentage
Curability	R0	58	69
	R1	25	29.8
	R2	2	1.2
Tumor diameter (cm)	Median; range	3.0; 2 - 12	
Grading tumor	G1 – G2	18 – 47	21.4 – 60
	G3 – G4	15 - 4	17.9 – 0.7
Satellites nodules	Present	10	11.9
	Absent	74	88.1
Macroscopic vascular invasion	Present	49	58.3
	Absent	35	41.7
Microscopic vascular invasion	Present	66	78.6
	Absent	18	21.4
Perineural infiltration	Present	69	82.2
	Absent	15	17.8
Pathological Tumor classification*	I	6	6
	IIA – IIB	16 – 15	22.6 – 17.9
	III	38	45.2
	IV	7	8.3
Number lymph node harvested	Median; range	7; 1 – 27	
Lymph node status	N0	40	47.6
	N+	44	52.4
Number lymph node positive	Median; range	3; 1 - 10	
Pathological Node classification*	N0	40	47.6
	N1	35	41.7
	N2	9	10.7
TNM Stage*	I	6	7.2
	II	23	27.3
	IIIA - IIIB	12 - 26	14.5 – 30.8
	IVA	7	8.3
	IVB	10	11.9

* Classification according to UICC/AJCC Cancer Staging System, TNM 7th Edition.

Median follow up was of 29 months (range 4-107). Median overall survival was 28.8 months; cumulative proportion survival at 3 and 5 years were 43.2% and 23.9% respectively.

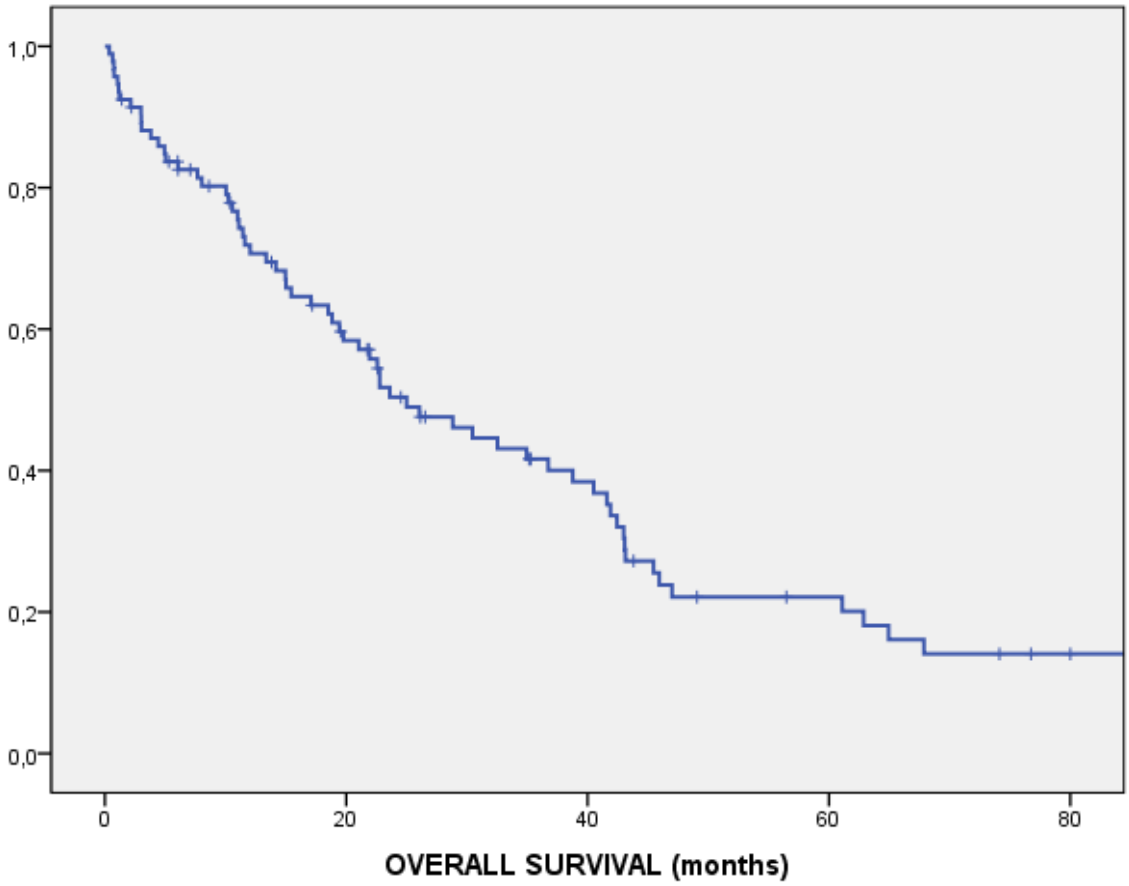


Fig. 2 Overall survival in patients submitted to radical resection for PCC

Univariate analysis of different clinical variables is reported in Table 4. Preoperative serum level of Ca 19.9 and CEA, resulted as positive prognostic factors for longer survival.

Table 4: Univariate analysis of clinical variables collected of patients with PCC. CI: Confidence interval.

		Median survival (95% CI)	***3y survival***	***5y survival***	***p-value***
Gender	Female	42.05 (21.3-62.8)	40.9%	24.5%	0.52
	Male	30.9 (20.9-40.9)	28.6%	14.7%	
Liver status	Normal	23 (19-28)	39%	24%	0.72
	Pathological	42 (5-79)	65%	43%	
Symptoms	Present	28 (10-47)	47%	32%	0.3
	Absent	22 (16-29)	34%	17%	
Biliary drainage	Positioned	34.8 (26-43.6)	43.4	19.7	0.57
	Not positioned	42.1 (30-54.4)	46.8%	26.3%	
CEA (ng/dL)	≤5	40 (31-50)	56.3%	28.1	**0.01**
	>5	16 (0-32)	16%	-	
CA 19.9 (U/mL)	≤500	41 (32-49)	57.5%	25%	**0.005**
	>500	19 (9-28)	0.9%	-	

From surgical variables (Table 5) major hepatectomy, caudate lobe resection, portal vein resection and reconstruction, and lymph node dissection were positive prognostic factors for longer survival. Patients who underwent major hepatectomy associated to common bile duct resection reached longer survival than patients submitted to only CBD resection or to minor liver resection with median survival of 40 and 18 months (p=0.04), respectively. Median survival, when caudate lobe resection was performed, was 36 months instead of 15 months (p=0.05). Median survival of patients without lymph node dissection was 7 months and no one patient reached 3 years survival. Median survival of patients, in whom resection and reconstruction of portal vein was necessary, had a shorter survival with a median survival of 15 months compared to 35 months for patients without vascular resection (p=0.001).

Table 5: Univariate analysis of surgical variables of patients with PCC. CBD: common bile duct. S1: caudate lobe. CI: confidence interval.

		Median survival (95% CI)	***3y survival***	***5y survival***	***p-value***
Liver resection	Associated to CBD resection	37(27-46)	48%	19%	0.14
	Not performed	18 (17-52)	17%	0%	
Hepatectomy	Minor/only CDB	18 (12-24)	27%	0%	**0.04**
	Major	40 (17-52)	48%	35%	
S1 resection	Performed	36 (17-56)	51%	31%	**0.05**
	Not performed	15 (8-22)	16%	0%	
LN dissection	Performed	28 (13-44)	46%	29%	**0.001**
	Not performed	7 (0-15)	0%	0%	
Vascular resection	Performed	15 (3-27)	18%	5%	**0.001**
	Not performed	35 (12-57)	48%	31%	

From pathological variables (Table 6) presence of satellites nodules was related of short term survival, with median survival of 6 months (p=0.001) and no one patient live at 5 years. Pathological tumor stage I and II combined had a median survival of 42 months compared to 15 months of stage III and IV combined (p=0.002). Extension of lymph node dissection results to be a protective prognostic factor: patients with more than 10 LNs harvested had a significantly longer median survival (37 months instead of 19 months) compared to patients with less than 10 LNs harvested (p=0.002). Lymph node status was a significant prognostic factor: patients with positive LN had a shorter survival (15 months instead of 28 months for patients without LN metastasis; p=0.04). Number of positive LN resulted to be a prognostic factor: patients with more than 3 positive lymph nodes had a shorter survival compared to patient without positive lymph nodes or with less than 3 positive lymph nodes, with median survival of 11, 43 and 35 months, respectively (p=0.01). Also lymph node ratio could significantly differentiate prognosis of patients (p=0.01); patients with LNR inferior to 0.25 had a longer survival than patients with LNR greater than 0.25 and similar to patients with LNR equal to 0 (p=0.19). Also pathological node stage (N0, N1, N2) according to TNM UICC/AJCC 7th classification was a strong prognostic factor for survival (p<0.001).

Table 6: Univariate analysis of histological variables of patients with PCC. CI: confidence interval.

		Median survival (95% CI)	***3y survival***	***5y survival***	***p-value***
Curability	R0	36(24-48)	44%	20%	0.44
	R1	21 (10-31)	41%	10%	
Grading tumor	G1 – G2	35 (13-57)	47%	33%	0.98
	G3 – G4	25 (9-40)	35%	23%	
Tumor diameter	≤3 cm	42 (15-68)	52%	36%	0.32
Satellites nodules	Present	17 (5-30)	17%	-	**0.05**
	Absent	38 (29-46)	56%	17%	
Macroscopic vascular invasion	Present	23 (19-28)	38%	34%	0.87
	Absent	42 (17-66)	54%	24%	
Microscopic vascular invasion	Present	35 (20-50)	46%	41%	0.92
	Absent	42 (10-74)	59%	29%	
Perineural infiltration	Present	26 (12-39)	43%	36%	0.35
	Absent	22 (7-38)	40%	0%	
Glissonian infiltration	Present	36 (19-54)	56%	34%	0.96
	Absent	26 (1-56)	48%	31%	
Pathological Tumor stage*	I-II	42 (31-53)	51%	27%	**0.002**
	III-IV	15 (11-26)	16%	11%	
Number LN harvested	<10	19 (13-28)	25%	9%	**0.002**
	>10	37 (NA)	70%	56%	
Lymph node status	N0	28 (19-61)	49%	28%	**0.04**
	N+	15 (11-36)	20%	13%	
Number N+ harvested	0	43 (41-44)	60%	35%	**0.01***
	1-3	35 (20-50)	48%	39%	
	>3	11 (7-15)	0%	0%	
Lymph node ratio	0	43 (41-44)	60%	35%	**0.01**
	0-0.25	26 (16-35)	41%	-	
	>0.25	11 (0-31)	0%	0%	
Pathological Nodal stage*	N0	43 (41-44)	60%	35%	**<0.001**
	N1	20 (3-37)	25%	-	
	N2	22 (1-19)	22%	0%	

* Classification according to UICC/AJCC Cancer Staging System, TNM 7th Edition.

The multivariate analysis confirmed the serum value of Ca 19.9 higher than 500 U/L, and the presence of positive lymphnodal involvement as factor strongly related to survival (table 7).

Table 7:Multivariate analysis of histological variables of patients with PCC. CI: confidence interval.

	HR	IC 95,0%		
Ca 19.9 > 500	4.9	2.05	11.7	0.001
N+	0.18	0.16	0.48	0.005

Patients with intrahepatic cholangiocarcinoma

During the study period 84 patients were submitted to liver resection with curative intent. These patients comprised 48 men and 35 women with a mean age of 66.13 years (range 40–85 years). Tables 8 and 9 list the patients' characteristics and the type of operative procedures performed, respectively.

*Table 8. Clinical c*haracteristics *of patients submitted to curative surgical resection for ICC. IG: intraductal growth type; MF: mass-forming type; PI: periductal infiltrating type*

Characteristic	**N (%)**
Male	48 (57.8)
Female	35 (42.2)
Macroscopic tumor growth type	
IG	3 (3.6)
MF	72 (83.7)
MF + PI	5 (5.8)
PI	3 (3.6)
Major liver resection	
Yes	33 (39.8)
No	50 (60.2)
Radicality	
R0	72 (86.7)
R1	11 (13.3)
Intrahepatic metastases	
No	55 (66.3)
Yes	28 (33.7)
Positive lymph node metastases	
No	53 (63.8)
Yes	30 (36.2)
T stage (TNM)	

T1-T2	65 (78.3)
T3-T4	18 (21.7)
TNM stage	
I-II	49 (59)
III-IV	34 (41)

Table 9. Surgical procedures in the 84 patients subjected to curative liver resection for ICC.

Procedure	**No. %**
Segmentectomy	16 (19)
Bisegmentectomy	7 (8.3)
Left hepatectomy (S2+S3+S4)	21 (25)
Left trisectionectomy (S1+S2+S3+S4+S5+S8)	1 (1.2)
Right hepatectomy (S5+S6+S7+S8)	35 (41.7)
Right trisectionectomy (S1+S4+S5+S6+S7+S8)	2 (2.4)
Central hepatectomy (S1+S4+S5+S8)	2 (2.4)
Total	

A R0 resection was achieved in 72 patients (86.7%). Extrahepatic bile duct resection was performed in 6 0(9.8%) patients in whom the tumor was judged to have invaded the biliary confluence. Vascular resection and reconstruction was necessary in one patient (1.6%).

There were 3 (1.6%) in-hospital deaths (class V according to the Dindo classification) after surgical resection and a postoperative morbidity rate of 29.5% (18 patients, Dindo class II in 15%, IIIa in 10%, IIIb in 4%, and IVa in 2%). The most frequent complications observed were biliary fistula (10%), abdominal abscesses (9%), pleural effusions (7%), liver failure (4%), and cholangitis (2%).

The overall median survival time was 31.8 months, with 3- and 5-year actuarial survival rates of 44.5% and 26.8%, respectively.

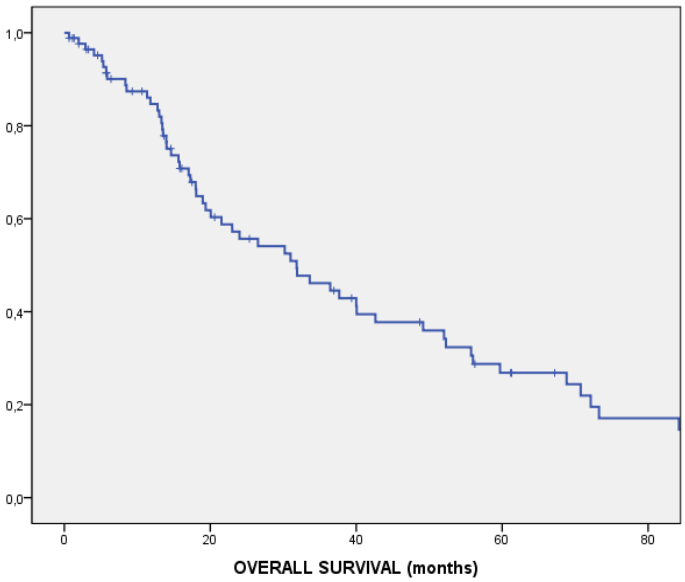


Fig. 3. Overall survival in patients submitted to radical resection for ICC.

Univariate Analysis

Among the 10 variables considered at univariate analysis, the CEA > 5 ng/dL, the presence of lymph node metastases, macroscopic vascular invasion, the presence of intrahepatic metastases, an higher grade of differentiation, an higher TNM stage and positive resection margins (R +) were significantly related to survival (Tables 10). Patients with R0 resections showed a 5- year survival rate of 31.5% compared to 12.1% for those with an R1 resection. Also, patients with positive lymph nodes had a significantly shorter survival compared to patients with negative lymph nodes; their median survival times were 55.4 and 26.8 months, respectively.

Table 10. Univariate analisys of clinical and pathological feature for patients submitted to surgery for ICC.

Factor	**Survival**			
	Median	**3-year**	**5-year**	
CA 19.9 (U/dL)				0.3
<500	45.6	52.1	34.1	
>500	19.4	26.7	-	
CEA (ng/dL)				0.001
<5	48.4	58.6	37.4	
>5	12	-	-	
Radicality				0.03
R0	52.5	51.3	31.5	
R1	25.9	42.2	12.1	

Lymph node metastases				
No	55.4	63.4	39	0.04
Yes	26.8	35.6	8.9	
Macroscopic vascular invasion				0.02
No	56.6	58.3	37	
Yes	30.6	34.4	10.7	
Perineural invasion				0.56
No	58.3	60.5	43.3	
Yes	38.3	43.3	19.8	
Intrahepatic metastases				0.03
No	55.2	56.2	34.9	
Yes	29.2	31.5	13.1	
Histologic grading				0.02
G1-G2	48.4	59.8	31.9	
G3-G4	22.8	0.8	-	
T stage (TNM)				0.9
T1-T2	47.8	47.9	29.1	
T3	41	50.8	20.3	
TNM stage				0.05
I-II	53.7	53.2	34.5	
III –IV	33.4	40.5	14.2	

Cox's regression multivariate model identified the high serum value of CEA, the presence of intrahepatic metastases and the radicality as being significantly related to survival with hazard ratios (HR) of 9.8, 2.2 and 2.3 , respectively (Table 11).

Table 11. Multivariate analisys of clinical and pathological feature for patients submitted to surgery for ICC.

	HR	IC 95,0%		
CEA>5	9,8	2.187	44.153	0.003
Intrahepatic metastases	2,2	1,182	4,093	0,013
Radicality	2.3	1,099	4,742	0,027
Macroscopic vascular invasion	1,745	0,917	3,321	0,090

Gross appearance and patient survival

Among the 83 patients of the resection group, the MF type was present in 72 (83.7%), MF+PI type in 5 (5.8%), PI type in 3 (3.6%), and IG type in 3 patients (3.6%). The type of surgery was not significantly

different among the gross types, although the rate of major resection was higher for the MF type. Kaplan-Meier survival analysis identified that survival was significantly related to the gross type, with median survivals of 51.9 months for patients with the MF type, 27.7 months for the MF + PI type, 35.3 months for the PI type, and 11.5 months for the IG type (Table 12).

Table 12. Survival rates between different type of ICC.

Factor	Median	3-year	5-year
MF	51.9	47	29.2
IG	35.3	33.3	-
PI	11.5	-	-
MF+PI	27.7	33.3	-

PI vs all p<0.05

Also, the rate of R + resection was significantly higher for the MF type (Table 13). Also the serum level of Ca 19.9 was significantly higher in the MF tumors. (Table 6).

Table 13. Univariate analysis for different type of ICC

	MF	PI	IG	MF+PI	p
CA 19.9 (U/L)					0.02
<500	44	2	1	3	
>500	4	1	2	2	
CEA					0.13
<5	39	1	0	3	
>5	8	2	3	0	
Radicality					0.03
R0	64	2	2	4	
R1	8	1	1	1	
Lymph node metastases					0.51
No	38	1	1	1	
Yes	34	2	2	4	
Macroscopic vascular invasion					0.74
No	40	1	2	2	

Yes	32	2	1	3	
Perineural invasion					0.51
No	32	0	0	1	
Yes	40	3	3	4	
Intrahepatic metastases					0.56
No	47	3	2	4	
Yes	25	0	1	1	
Histologic grading					0.74
G1-G2	34	2	2	3	
G3-G4	12		1	2	
T stage (TNM)					0.10
T1-T2	60	1	3	1	
T3-T4	12	2	0	4	
TNM stage					0.42
I-II	46	1	1	1	
III -IV	26	2	2	4	

Prognostic factors for recurrence after surgical treatment

Regarding the patients affected by ICC, (50.8%). The 1-, 3- and 5- year disease-free survival was 61.1%, 29.2% and 29.2%. Recurrences were mostly located into the liver (16 patients, 51.6%), followed by peritoneum (5 patients, 16.1%) and lung (3 patients, 9.7%). Multifocal recurrence occurred in 6 patients (19.4%, table 15).

Table 15. Recurrence site of patients submitted to surgery for cholangiocarcinoma.

Recurrence site	**Patients ICC**	**%**	**Patients PCC**	**%**
Intrahepatic	16	5.6	8	19.0
Intrahepatic and lymph-nodal	-	-	4	9.5
Bilio-digestive anastomosis	1	3.2	4	9.5
Peritoneal carcinomatosis	5	16.1	9	21.5
Lung	3	9.7	5	12.0
PTBD site	-	-	4	9.5
Multifocal	6	19.4	8	19.0
Total	31	100,0	42	100,0

Univariate analysis in patients affected by ICC showed the following factors related to recurrence: a preoperative serum level of Ca 19.9 higher than 50 U/mL, the absence of histological radicality, a higher histological grading, a tumor size higher than 30 mm, the presence of tumor multifocality (table 5). The Cox regression model identified the histological grading as factor significantly correlated to recurrence (table 5).

Regarding the patients affected by PCC, the 59.2% of patients (42 patients) developed a recurrence after the surgery. Recurrence occurred as intrahepatic in 12 patients (28.5%), as extra hepatic in 30 patients (71.5%). The site of recurrence is shown in details in table 4. The 1-, 3- and 5- year disease-free survival was 77.5%, 34.4% and 18.4%.

At univariate analysis a preoperative serum level of CEA > 5 mg/dL, the resection and reconstruction of portal vein, the presence of multifocality, a lymph-node ratio >0.25 and the presence of perineural invasion were the factors significantly related to recurrence (table 5). At multivariate analysis, the resection and reconstruction of portal vein and the lymph-node ratio<0.25 were confirmed to be prognostic factors related to recurrence (table 16).

Table 16. Univariate and multivariate analysis of prognostic factors related to recurrence. PV: portal vein

	ICC patients (n=31)					
	Median DFS survival	*Univariate analysis p*	*Multivariate analysis p*	Median DFS survival	*Univariate analysis p*	*Multivariate analysis p*
Age		0.16	-		0.98	-
< 65	43.2			19.2		
>65	11.9			20.0		
Gender		0.75	-		0.63	-
F	58.5			36.2		
M	37.1			29.0		
Ca 19.9		0,045	-		0.49	-
<50 U/mL	16.4			20.7		
>50 U/mL	10.7			20.0		
CEA		0.068	0.039		0.043	-
< 5 mg/dL	29.7			30.1		
> 5 mg/dL	9.9			18.0		
Preoperative jaundice		0,97	-		0.47	-
Yes	31.3			39.6		
No	25.3			20.8		
Tumor size		0.043	-		0.31	-
< 30 mm	16.4			20.8		
> 30 mm	9.9			13.9		
Resection/reconstruction of PV		--	-		0.035	0.001
Yes	--			13.3		
No	16.4			20.8		
Radicality		0.05	-		0.265	-
R0	17.5			24.0		
R+	6			20.8		
Caudate lobe resection		0.7	-		0.023	0.012
Yes	16.4			20.8		
No	11.9			13.9		
Multifocality		0.001	-		0.031	-
Yes	7.4			5.3		

No	26.4			20.0		
Grading		0.04	-		0.91	-
G1-G2	20.9			30.1		
G3-G4	9.1			20.0		
Lymph-node ratio		0.115	-		0.032	0.047
<0.25	16.2			18.6		
>0.25	6.2			6.7		
Perineural invasion		0.74	-		0.014	-
Yes	17.5			17.8		
No	24.0			37.7		

Treatment of recurrence

Among patients affected by ICC, 20 patients were submitted to treatment for the recurrence. Six patients underwent surgical resection of recurrence (19.6%, table 6) and chemotherapy was performed in 14 patients (45.2%). The remnant 11 patients received best supportive care.

Forty-seven (78%) patients with PCC who developed a recurrence were submitted to some kind of treatment: 9 (19.1%) patients were submitted to re-surgery (table 7), 29 patients were submitted to chemotherapy (61.8%, of whom 2 were submitted to radiotherapy). Nine patients (19.1%) received best supportive care.

Table 17 . Surgery with curative intent for recurrence in patients with ICC

	Patients
Intrahepatic resection	5
Segmentectomy S1	1
Segmentectomy S4	1
Segmentectomy S5	1
Segmentectomy S8	1
Segmentectomy S8 + PEI	1
Resection of abdominal wall nodule	1

Table 18 . Surgery with curative intent for recurrence in patients with PCC

	Patients
Intrahepatic resection	3

Segmentectomy S4	1
Segmentectomy S5	1
Segmentectomy S8	1
Resection of abdominal wall nodule (PTBD site)	2
Resection of peritoneal nodule	2
Pancreatoduodenectomy	1
Sigma resection	1

We further analyzed the survival after treatment of recurrence. For all patients, the 1- and 3- year actuarial survival was 38% and 18%, respectively. Depending on treatment, the patients submit to surgical resection of recurrence showed a 1- and 3- year actuarial survival of 64.8% and 25.9%. The patients treated with chemo- or radiotherapy showed a 1- and 3- year actuarial survival of 60.3% and 18.8%, respectively. The patients who received best supportive care showed a 1- and 3- year actuarial survival of 16.7% and 0%, respectively. This difference showed a statistically significance difference (p=0.005, fig. 2).

In patients affected by ICC, the median survival after recurrence was 11.6 months. Depending on treatment, the patients submit to surgical resection of recurrence showed a 1- and 3- year actuarial survival after recurrence of 83.3% and 41.7%, respectively. Those treated with chemo- or radiotherapy showed a 1- and 3- year actuarial survival after recurrence of 46.4% and 15.5%, respectively. Who received best supportive care showed a 1- and 3- year actuarial survival after recurrence of 33.3% and 0%, respectively. This difference showed a statistically significance difference (p=0.014, fig. 3).

In patients affected by PCC, the median survival after recurrence was 6.3 months. Depending on treatment, the patients treated with chemo- or radiotherapy showed a 1- and 3- year actuarial survival of 61.1% and 22.9%, respectively. Those submit to surgical resection of recurrence showed a 1- and 3- year actuarial survival of 33.3% and 0%. No patient who received best supportive care survived beyond 9 months. Nevertheless, this difference did not reached a statistically significance difference (p=0.069, fig. 4).

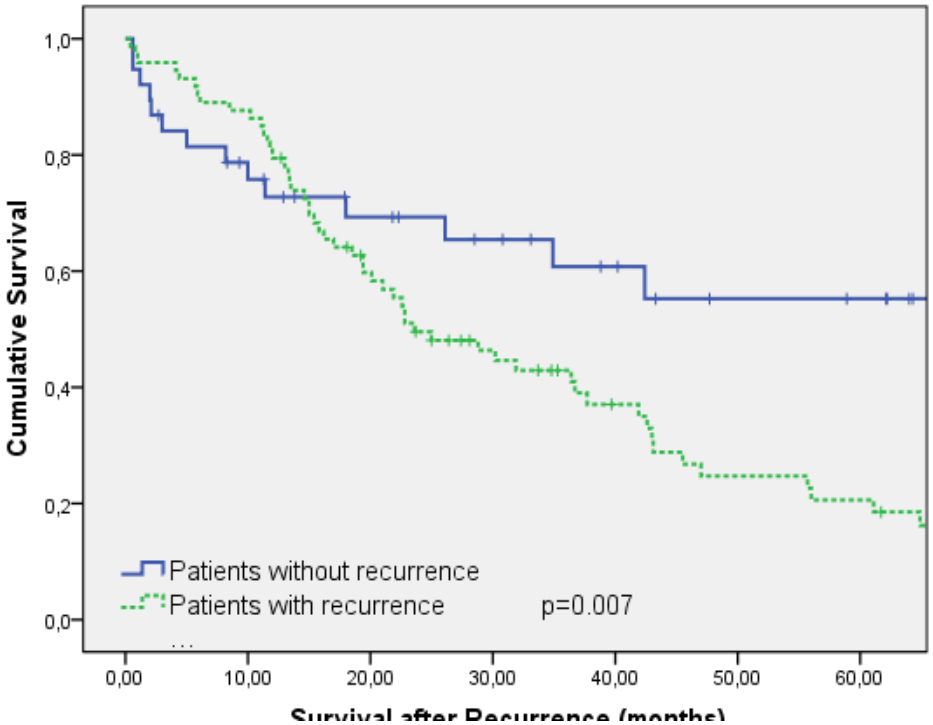


Fig 4. Overall survival for patients submit to surgery with curative intent for ICC and PCC according to onset of recurrence (p=0.007).

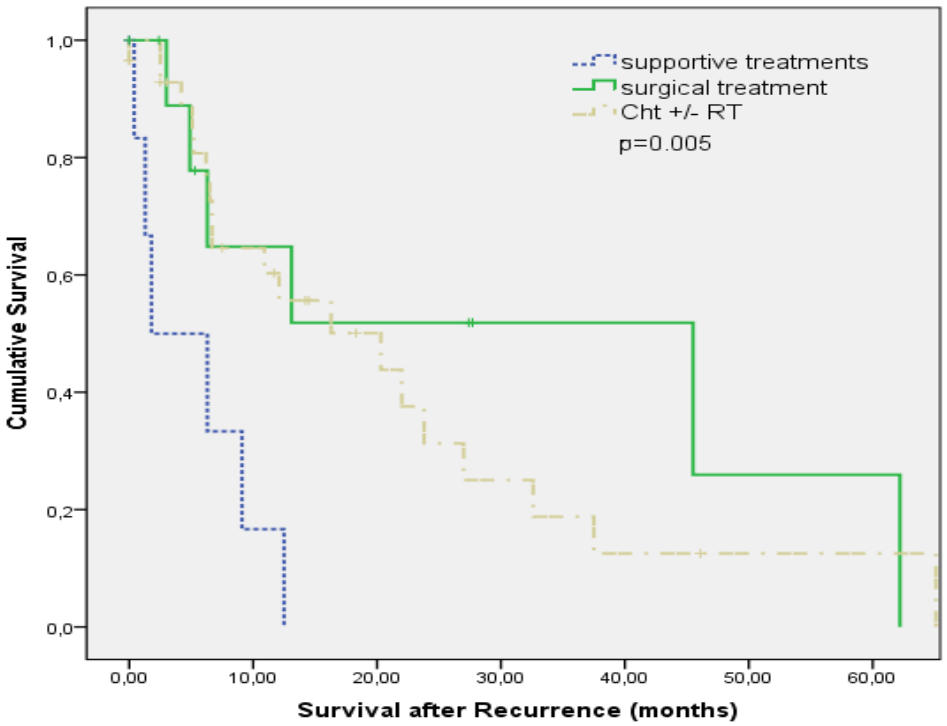


Figure5. Survival after different treatment of recurrence in both groups (ICC and PCC) of patients (p=0.005).

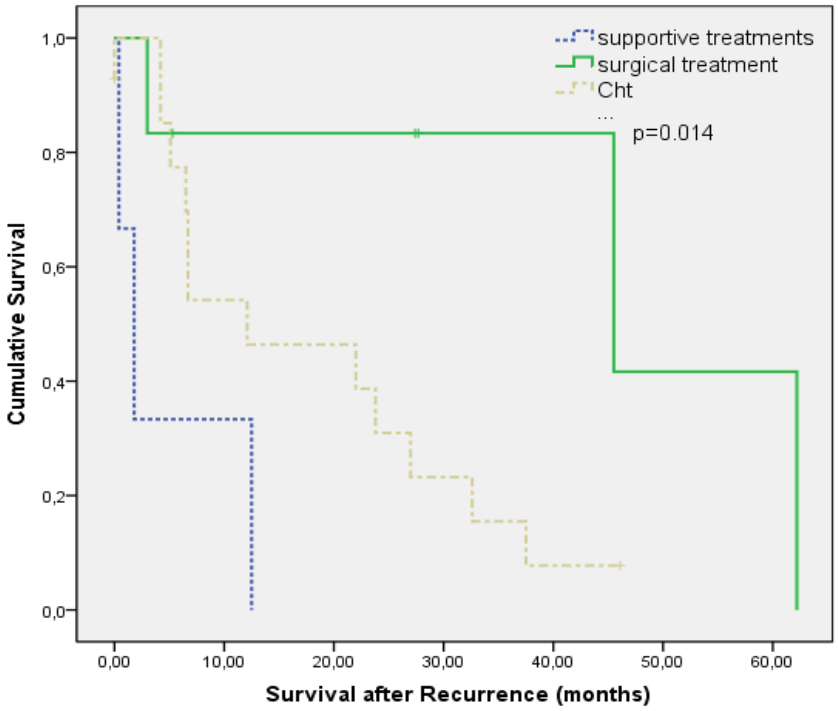


Figure 6. Survival after different treatment of recurrence in patients with ICC (p=0.014).

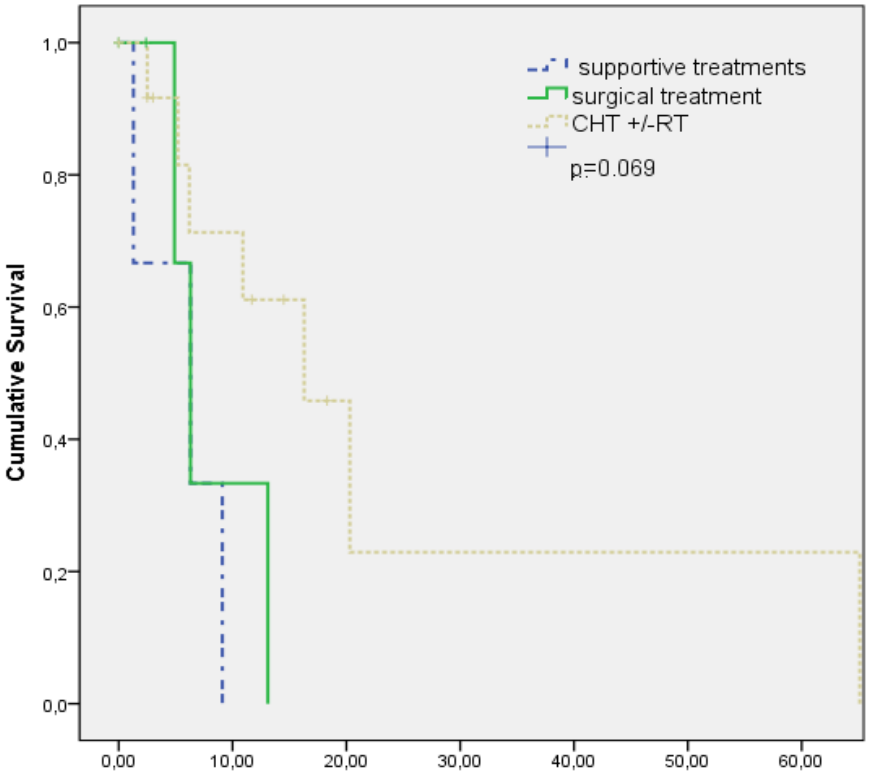


Figure 7. Survival after different treatment of recurrence in patients affected by PCC (p=0.069).

Comparison over the periods before and after 2005

Finally, we performed a comparison among patients submitted to surgery with curative intent before and after 1st January, 2005.

Among patients affected by PCC, 29 were submitted before 2005 and 55 after 2005 (table 19).

In patients submitted to surgery after 2005 compared to those submitted before 2005 the age was significantly higher (90.5% of patients were elder than 60 years old compared to 61.7%, respectively, p=0.005). The use of preoperative biliary drainage was significantly increased (61.9% vs. 35.3%, respectively, p=0.006). Regarding the intra-operative issues, in the group of patients treated after 2005 compared to patients underwent before 2005 the rate of associated hepatic resection was higher (78.6% vs. 67.6%) and more major hepatectomies were performed (73.8% vs. 64.7%).

The rate of caudate lobe resection was higher in patients treated after 2005 (71.4% vs. 58.8%). Despite the more extension of resection, mortality was similar in the two groups (7% vs. 8%, p=1.0). The R0 resection was reached in 61.9% and 55.9% after and before 2005, respectively (p=0.07).

Even if lymphadenectomy was similarly performed in the two groups, only 26.5% of patients received an harvesting of more then 3 lymph-nodes before 2005 respect to the 76.2% after 2005 (p=0.001) with a mean 2.49 and 6.17, respectively. The 5-year overall survival was significantly increased before and after 2005 (12.5% and 39.4%, respectively, p=0.01). In patients submitted to surgery after 2005 respect than in those treated before 2005, it is shown a lower recurrence rate (51.7% vs. 78.9%, p=0.07) and a higher 3-year disease-free survival (49.6% vs. 26.3%, respectively, p=0.01, fig. 8).

Remarkably, in patients submitted to surgery after 2005 with radical resection and with no positive lymph-nodes metastases, the 5-year survival was 73.8%, compared to 13.6% of the same patients submitted to surgery before 2005 (fig. 9).

Table 19. PCC Patients' characteristiscs regarding the period of teatment.

	Before 2005 (n=29)	**After 2005 (n=55)**	**p**
Age			<0.01
<60 years	11 ()	10 ()	
>60 years	18 ()	45 ()	
Preoperative biliary drainage			<0.01
Yes	11 ()	36 ()	
No	18()	29 ()	
Ca 19.9			0.16
<500 U/mL	3 (	36 (	
>500 U/mL	3 (	10 (	
Tumor size			0.07
< 30 mm	9 ()	20 ()	
> 30 mm	9 ()	26 ()	

Associated Hepatectomy			0.30
Yes	21 ()	4 ()	
No	8 ()	51 ()	
Major Hepatectomy			0.07
Yes	22 ()	46 (73.8%)	
No	2 ()	6 (26.2%)	
Portal Resection/Reconstruction			0.5
Yes	5 ()	11 ()	
No	24 ()	44 ()	
Caudate lobe resection			0.19
Yes	20 ()	44 (71.4%)	
No	9 ()	11 (28.6%)	
Lymphadenectomy			0.17
Yes	26 ()	54 ()	
No	3 ()	1 ()	
More than 3 LN harvested			<0.01
Yes	9 (26.5%)	32 (76.2%)	
No	25 (73.5%)	10 (23.8%)	
R0 resection			0.03
Yes	19 (58.9%)	26 (6.,9%)	
No	15 (44.1%)	16 (38.1%)	

Fig.8Comparison of overall survival between patients submitted to resection before 2005 (red line) and after 2005 (green line), p<0.05.

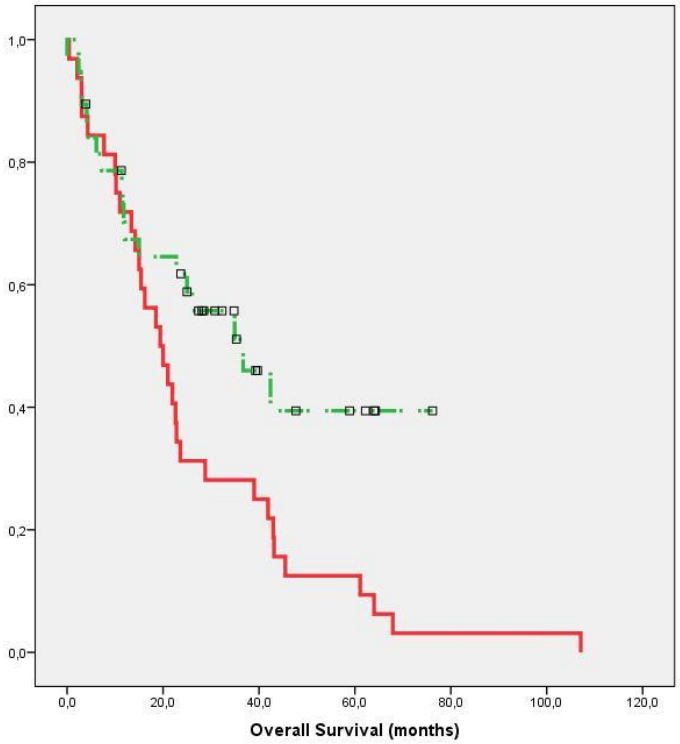
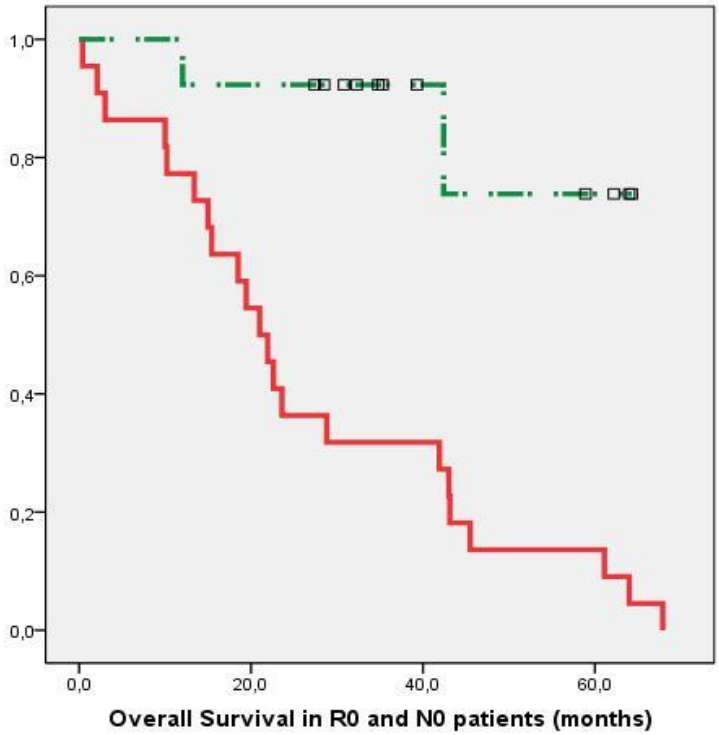


Fig.9 Comparison of overall survival between patients submitted to R0 resection before 2005 (red line) and after 2005 (green line),



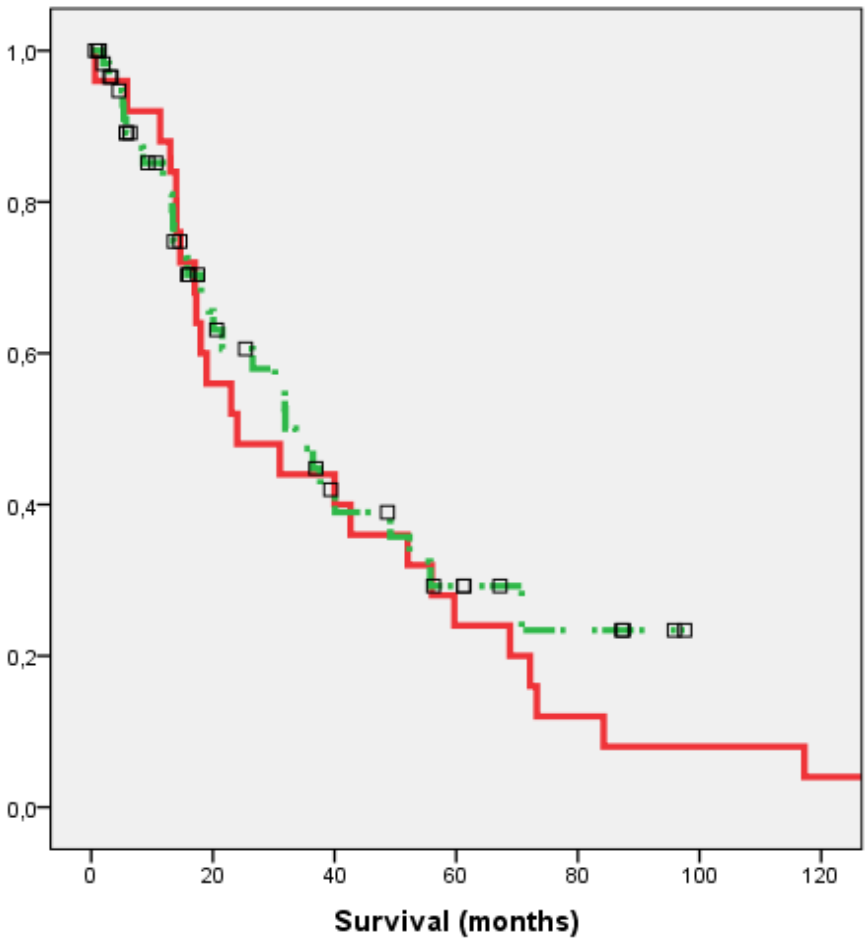
In patients affected by ICC, 25 were submitted to surgery before and 58 after 1st January, 2005. Patients were older after 2005. Tumor seemed to be more advanced after 2005: indeed, the tumors were bigger in size and with more macrovascular involvement rate in patients submitted to surgery after 2005 than in patients submitted before 2005. So, the surgery resulted more aggressive after 2005, with more major hepatectomy and more lymph node harvested than before, even if with no difference in complication rate between the two periods. R0 resections were more performed after 2005 than before.

	Before 2005 (n=25)	**After 2005 (n=58)**	**p**
Age			0.05
<60 years	11 (44%)	12 (20.7%)	
>60 years	14 (66%)	46 (79.3%)	
Ca 19.9			0.62
<500 U/mL	19 (76%)	47 (81%)	
>500 U/mL	6 (24%)	11 (9%)	
CEA			0.46
<5 ng/dL	16 (64%)	43 (74.1%)	
>5 mg/dL	9 (36)	15 (25.9%)	
Tumor size			0.001
< 30 mm	8 (32%)	7 (12%)	
> 30 mm	17 (68%)	51 (88%)	
Macrovascular Involvement			0.003
Yes	5(20%)	26 (44.8%)	
No	20 (80))	32 (55.2%))	
Major Hepatectomy			0.07
Yes	22 (88%)	49 (84.5%)	

No	3 (12%)	9 (15.5%)	
Portal Resection/Reconstruction			0.5
Yes	3 (12%)	14 (24.1)	
No	22 (88%)	44 (75.9)	
Microvascular Involvement			0.001
Yes	14 (56%)	43 (74.1%)	
No	9 (44%)	12 (25.9%))	
Lymphadenectomy			0.101
Yes	23 (92%)	54 (93.1%)	
No	2 (8%)	4 (6.9%)	
More than 3 LN harvested			<0.01
Yes	9 (44%%)	39 (67.2%)	
No	14 (66%)	19 (32.8%)	
R0 resection			0.03
Yes	15(60%)	44 (81%)	
No	10 (40%)	11(9%)	
Postoperative complications			0.53
Yes	17 (68%)	39 (67.2%)	
No	8 (32%)	19 (32.8%)	

Nevertheless, these results did not allow a survival gain in patients before and after 2005 (p=0.48, fig 10).

Fig.10 Comparison of overall survival between patients submitted to resection before 2005 (red line) and after 2005 (green line), p=0.48,


1,0
0,8
0,6
0,4
0,2
0,0
0
20
40
60
80
100
120
Survival (months)

Discussion

Cholangiocarcinoma is the second most frequent primary liver tumor and its incidence is increased in Western countries in last 30 years [3].

Perihilar cholangiocarcinoma is defined as biliary tumor originating and located in the biliary confluence and extending to extrahepatic biliary tree either to intrahepatic parenchyma [7] . Perihilar cholangiocarcinoma is rarely operable and even when surgical operation is feasible long term survival is dismal but surgical resection is the only chance to cure this aggressive disease [63] . Surgical management is demanding, however recent aggressive surgical operations could reach good long-term survival [63].

Different clinicopathological factors have been previously evaluated and related to survival: radical resection, vascular invasion, tumor size, multifocality, tumor grading, perineural invasion, lymph node metastasis, tumor stage and positive resection margins [10, 64-70] .

In our study we evaluated several clinical and pathological variables of patients submitted to surgical resection with radical intent. From univariate and multivariate analysis the serum Ca 19.9 preoperative value greater than 500 U/mL was a significant prognostic factor for survival reflecting biological behaviour of tumor. CA 19.9 is a tumor marker increased in other gastrointestinal tumors; also in others series of patients with perihilar cholangiocarcinoma was related with poor prognosis [71, 72] [73] . CA 19.9 is an easily available test laboratory that could correlate with poor survival and especially it's available preoperatively. Also from our data, aggressive treatment reach longer survival; indeed, major hepatectomy, caudate lobe resection and lymph node dissection were significant prognostic factor for longer survival. Lymph node metastasis is a strong prognostic factor and was already evaluated in literature [20, 63, 64, 66, 74] . Lymph node metastasis is a prognostic factor per se but patients with low value lymph node ratio (<0.25) have survival similar to patients without positive lymph node. For this reasons we suggest to perform an extensive lymph node dissection to better stratify patients. Patients with more than 10 lymph node harvested had a significantly longer survival. In literature extension of lymph node dissection is still under discussion, however recent studies are giving important additional data about that [64] [75] .

In our analysis the 3- and 5-years cumulative survival rate were 43.2% and 23.9% respectively. These results are consistent with those available in literatures [50, 66, 76].

Intrahepatic cholangiocarcinoma (ICC) is the second primary liver cancer after HCC and it accounts for 3% of all gastrointestinal cancers and usually it presents as a mass inside the liver [24].

The macroscopic pattern of growth of the ICC (MF , PI, GI) reflects the different biological behavior and tumor spread. The MF type is the most frequent (60-70% of cases), it is associated with an early portal invasion in 45% of cases and satellite nodules are present in 36% of cases. The lymph node involvement is present in approximately 30%. The 5-year survival reported in the literature varies between 25% and 48% [24, 77]. Among all resected ICC, the IG type is found in 8% to 23% of cases. It presents as a papillary-like tumor and it is well differentiated in most cases with a low frequency of lymph-nodal, vascular or perineural invasion. The long-term survival of patients with IG-ICC after surgical resection is good, with a 5-year survival of 40-80%. The survival of patients with the disease type IG is significantly longer than patients with MF and PI types, also in cases of lymph-nodal metastases [78]. The PI type has a worse prognosis than the other two types. This form is found in 15-35 % of cases and it is associated with biliary, vascular and lymphatic infiltration at the hepatic hilum. The 5-year survival in these patients is lower than 40% [79]. The mixed form MF + PI is found in 25%-45% of patients. This form has a worse prognosis because the diagnosis is presented with a more advanced stage of the disease, often with a higher frequency of lymph node metastases as well as vascular invasion and intrahepatic metastases. The long-term survival is poor, with less than 10 % of patients alive at 5 years [78]. Our results confirmed the rate reported by literature, indeed, the median survive of PI type is only 11.5 months, with no patients alive after 3 year from surgery.

The size of the tumor is an important factor that determine the prognosis: indeed, the 5-year survival in patients with a mass with less than 3 cm in size is 42%, while in patients with a mass greater than 6 cm the survival is reduced to 0% [80]. The presence of satellite nodules, in literature, have been reported in 20-30% of patients, with a poor 5-year survival (0-7%)[26, 80]. The portal infiltration is an important negative prognostic factor for the ICC: survival was significantly greater in patients without portal involvement than those who have macroscopic portal infiltration , with 3-year survival of 46% and 0% respectively[28]. In literature, the presence of lymph node metastases ranges from 7% to 73 %. It is a major prognostic factor for prognosis: patients with N+ have a 5-year survival between 0% and 20% [81]. The frequency of lymph node involvement in the forms IG is significantly lower than the other forms, while in the mixed type MF + PI is significantly higher: according to some series, lymph-nodal involvement does not exceed 20% in the former, while it reaches 80% in the latter. The lymph node involvement is also related to the stage of disease and, according to some studies, it is present in 80% of patients with advanced stage disease (T4) [55]. The frequency of lymph node metastases is related also to the site of the tumor: it is reported to be higher in tumors with hilar involvement than those with peripheral growth (75 vs . 45%, respectively) [27]. Our results are consistent with these results, univariated analysis showed that macroscopic vascular invasion, an higher

grade of differentiation, an higher TNM stage, positive lymph nodes, the presence of intrahepatic metastases, positive resection margins and the preoperative serum level of CEA > 5 mg/dL were poor predictors of survival. The latter three factors were also confirmed at multivariated analysis.

Recurrence is common even after R0 resection and arises in 40-80% of cases; it generally occurs early within 2 years 86. The most frequent sites of recurrence are: the liver (74%), the peritoneum (22%), lymph nodes and bone (11%)[55]. In literature, the following the factors are identified as related to recurrence: hilar involvement, size of the tumor, portal involvement, presence of lymph node metastases, high serum levels of Ca 19-9 [55]. Another factor related with the onset of high rate of recurrence is the macroscopic gross type of growth: the frequency of recurrence is significantly higher in PI forms compared to MF forms. The macroscopic type of growth affects also the site of recurrence: the MF ICC is particularly associated with an increased frequency of intrahepatic recurrences (68% of all recurrences), while the lymph-nodal recurrence is more frequent in the forms MF + PI and PI. The treatment of recurrence varies in function of its location and its extension; in most cases is only palliative. In isolated cases, it was possible to reach a long-term survival after resection of intrahepatic recurrence [46]. In very selected cases, also, the surgical treatment, including transplantation, has offered good results of long term survival [56, 82]. However, the clear indications on the proper treatment for recurrence, both surgical and palliative, have not yet been clearly established in the literature. Regarding the patients with ICC, the reported recurrence rate varies from 46% to 68% [67, 83, 84]. In our study we showed a rate of recurrence of 55.3%, with a 3 year disease-free survival of 29.2%. the location of recurrence is intrahepatic in 50-92% of cases [85]. Our case series corroborated these data, with a intrahepatic recurrences of 51.6%.

This study confirmed that the high preoperative Ca 19.9, the multifocality, the tumor size and the histological grade are the most significant prognostic factors for recurrence, as reported in literature [55, 86-88]. Particularly, the histological grading appeared significantly related to disease-free survival in univariate and multivariate analysis, as reported also by other Authors. Tamandl et al. [89] and Saiura et al.[88] showed that the tumor differentiation is a significant factor in univariate and multivariate analysis, with an HR of 7·02 and 2.01, respectively. Also Shirabe et al.[90] confirmed this finding in univariate and multivariate analysis, reporting a shorter 5-year recurrence-free survival in patients with poor tumor differentiation compared to patients with well or moderate tumor differentiation (57%, 52.7%, 23.2%, respectively).

This could be related to the biologic aggressiveness of the primitive tumor cells, which increases during the process of dedifferentiation.

In patients with PCC, the surgical resection is often limited by the contiguity with vascular structures and the high frequency of distant metastases at diagnosis. An aggressive surgical treatment, including resection of the liver parenchyma, the bile duct and, if needed, the vascular structures involved improved the overall survival rates, which are reported between 11% and 40% at 5 years with a median survival between 16 and 40 months, compared with a median survival of only 5 months in patients unsuitable to surgical resection[51, 65]. However, most patients (53-64%) develop a recurrence with a median disease-free survival of 15-20 months [67, 91].

We reported a recurrence rate of 59.2%, comparable with those reported in literature. Regarding the site of recurrence, we showed that the most are located as extrahepatic (71.5%), confirming the data of literature[67, 91].

In this report, the resection and reconstruction of portal vein, and a lymph-node ratio<0.25 were the factors significantly related to recurrence at univariate and multivariate analysis.

In patients with PCC, the rate of regional lymph nodes metastasis is reported between 16 and 56%. In a recent paper of our group [64] we demonstrated that lymph-node metastases is major prognostic factor in terms of survival, showing a median survival of 41.9 months in patients with N0 compared with 22.7 months in patients with N+ (p=0.03). Besides, the lymph-node ratio with a cut-off value of 0.25 was a strong prognostic value, with a 5-year survival for patients above and below this cut-off of 0% and 22.5%, respectively (p=0.03).

Kobayashi[91] described a 3-years recurrence rate statistically higher in patients with lymph node metastases than in patients without lymph node involvement (78% vs. 31%, respectively, p <0.001). These data are confirmed by Saxena et al.[67], showing a statistically significant difference in disease-free survival among patients with stage N0 and N+ (46 months vs. 39 months respectively, p = 0.03).

In the majority of patients with recurrence, further surgical resection is not possible for the poor general conditions of patients, for the impaired liver function of for the extension of the disease. However, in highly selected patients, a repeat liver resection seemed to be feasible. The majority of studies available in literature are concerning patients affected by ICC and reported small case series [92]. Interestingly, Ercolani et al., in a study including 38 patients affected by recurrence among 72 patients underwent surgical resection for ICC, showed 6 (17.6%) patients treated with hepatic resection and 8 (23.5%) patients treated with RFA for recurrence, with a 3-year survival rate of 60% compared to 0% of untreated patients with recurrence (p = 0.001).

When feasible, surgical treatment of recurrence in patients with ICC allowed a better survival in our series. The patients submit to surgical resection of recurrence showed a 3- year actuarial survival after recurrence of 41.7% respectively, significantly higher than survival in patients affected by recurrence treated with chemo- or radiotherapy or best supportive care (15.5% and 0%, respectively, p= 0.014). Nevertheless, in patients with PCC, this statement was not confirmed. The survival in patients submit to surgical resection of recurrence showed a 1- year actuarial survival of 33.3%, compared to 61.1% in patients treated with chemotherapy, although it did not reach statistically significance difference (p=0.069). Some reasons may explain that. First, the recurrence on patients with PCC appeared earlier and more frequent multifocal compared than patients with ICC. This fact did not allow a surgical treatment of recurrence with curative intent in most cases. Second, even if there are no consensus in literature, adjuvant chemotherapies in some studies [93, 94] showed encouraging results, with a significant improvement of survival rates in patients submitted to adjuvant treatment compared than patients not treated (actuarial 5-year survival of 57% and 24%, respectively, p<0.001).

Surgical treatment of cholangiocarcinoma has been evolving steadily, with expanded surgical indication, decreased mortality, and increased survival . Achieving R0 status, with concomitant liver resection as necessary, is the most important variable associated with outcome and long-term survival. Among patients who have had an R0 resection, lymph node status is likely the next most important prognostic factor[95]. Nagino[96] reported that the survival in PCC was significantly better in the later period of 2001 to 2010 than in the earlier period of 1977 to 2000 (38.1% vs 23.1% at year 5, P < 0.001). For R0, and pN0 patients (n = 243), the survival in the later period was 67.1% at year 5, which was significantly better than that of the earlier period (P < 0.001). Similarly, in patients with R0 and N0 resections, we obtained a better survival rate in the period after 2005, with a 5 year survival of 73.8% after 2005 compared to 13.8% before.

Conclusions

Surgery for perihilar and intrahepatic cholangiocarcinoma is demanding, with poor long term results. Confirming the results of literature, in patients with PCC we demonstrated that an low preoperative serum level of Ca 19.9 and CEA, major hepatectomy, caudate lobe resection, portal vein resection and reconstruction, and large lymph node dissection with more than 10 lymph nodes were positive prognostic factors for longer survival. Besides, perioperative and surgical thecniques for the treatment of PCC has been evolved during the years. In our institution, patients treated for PCC in the last 10 years gained a significantly better overall survival rates compared to patients treated before, especially if radical resections were performed with no lymph node involved.

Regarding patients with ICC, CEA > 5 ng/dL, the presence of lymph node metastases, macroscopic vascular invasion, the presence of intrahepatic metastases, an higher grade of differentiation, an higher TNM stage and positive resection margins (R +) were significantly related to survival. MF type demonstrated to have better prognosis than other types of ICC.

Recurrence is confirmed to be a major prognostic factor. Regarding patients with PCC, recurrences are often extrahepatic. The need of portal resection and a lymph-node ratio higher than 0.25, a preoperative high value of CEA, the perineural invasion and the multifocality are the prognostic factors related to recurrence. In patients with ICC, recurrence occurred as intrahepatic in the most of cases. The histological grading, a preoperative high value of Ca 19.9, the tumor size higher than 30 mm, the absence of radicality and the multifocality are the prognostic factor related to recurrence in patients with ICC. When feasible, aggressive surgical resection of recurrence can improve the prognosis in these patients, especially in patients with ICC. In patients with PCC, in which recurrence is more often unresectable, aggressive adjuvant treatment protocol could improve survival reducing the frequency of recurrences.

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