Review Article

Current and emerging treatments for cholangiocarcinoma

*Christopher Lim, Desmond Wai, KH Lee, KC Tan.

Asian Centre for Liver Diseases & Transplantation, Gleneagles Hospital, Singapore

***Correspondence to**
Asian Centre for Liver Diseases & Transplantation, 6A Napier Rd, # 02-37 Gleneagles Hospital Annexe Block, Singapore 258500, Fax: +65 64763088, E-mail: fluppy888@yahoo.com

Abstract

Surgical resection, the treatment of choice for cholangiocarcinoma, may not be feasible because of tumour extension, parenchymal liver disease or tumour location. Liver transplantation is an alternative to palliative treatment in these patients but results in the past have been disappointing. In this article, we review the current and emerging treatments for cholangiocarcinomas, focusing particularly on the role of neoadjuvant chemotherapy and/or radiotherapy in the setting of liver transplantation.

Keywords

Cholangiocarcinoma, biliary tract neoplasms, living donor liver transplantation, cadaveric donor liver transplantation.

Introduction

Cholangiocarcinoma (CCA) is an aggressive malignancy that arises from the epithelial cells of the biliary tree either within the hepatic parenchyma (intrahepatic) or extra-hepatically within the gastro-duodenal ligament. About 50–60% of tumours occur at the bifurcation of the left and right hepatic ducts (hilar CCA, 'Klatskin' tumour), 10% are intrahepatic and 20–30% are extrahepatic distal bile duct tumours.[1] CCA is the most common liver cancer after hepatocellular carcinoma and has an incidence of 1- 2 in 100,000 in the western population with a much higher incidence amongst the South East Asian demographic. The prognosis is dismal and average survival is 5 – 10 months.[2] There is currently no effective medical treatment and surgical resection, where possible, offers the only prospect for long-term survival. The median survival for unresectable cases undergoing chemotherapy or chemoradiation is 9 – 12 months.[3,4]

In this paper, we review the current and emerging treatments of CCA, focusing especially on liver transplantation (LT) in the light of promising survival data from the Mayo Clinic.[5]

Methods

We did a MEDLINE search on March 1, 2010 using the terms: cholangiocarcinoma, bile duct cancers, intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, hilar cholangiocarcinoma, Klatskin tumours, cholangiocellular carcinoma, liver transplantation, orthotopic liver transplantation, allograft liver transplantation, and living donor liver transplantation. Searches were limited to papers published in English. Case reports and those studies with less than 5 patients were excluded.

Chemotherapy

CCAs are relatively chemo-resistant, as such chemotherapy has been met with poor response rates. Trials of 5-fluorouracil have produced response rates of up to 10% with a median follow-up of 6 months. The most promising single agent appears to be gemcitabine with a response rate of 36%. Combination therapies have response rates of 31-40%.[6] In a meta-analysis by Eckel et al, gemcitabine plus platinum chemotherapy seemed to offer a slight advantage over other regimens.[7] However, median survival following combination chemotherapy for unresectable disease is still only about 9 to 12 months, and long-term survival is infrequent.

Resection

Surgical resection has been the mainstay of curative treatment for CCA in the absence of primary sclerosing cholangitis (PSC).[1] Resection in patients with PSC is discouraged as CCA is often multifocal and underlying parenchymal disease is common, resulting in death in

>90% of patients.[1] Liver resection with free margins (R0 resection) is the aim for peripheral cholangiocarcinoma (PCC) and for hilar CCA, it usually involves resection of the bile duct, which may be extended on occasions to a liver resection, depending on the location of the tumour, or a vascular resection.

Complete resection may be curative but the majority (70-80%) are unresectable due to the presence of advanced disease at the time of diagnosis, associated advanced liver disease, bilateral liver involvement, centrally located lesions, or vascular encasement.[1,8,9] Those who undergo resection have a 5-year survival ranging from 11% to 40%.[10-13] Negative surgical margins, non-involvement of lymph nodes, and tumour depth of T-2 or less were statistically significant good prognostic factors.[14] Patients with unresectable CCA usually receive palliative treatment and have very short life expectancies.

Locoregional recurrence in the region of the head of the pancreas is a frequently observed pattern after surgery and may occur after many years. Hence, some groups have introduced more radical techniques such as the pylorus-preserving cluster operation[15] and extended bile duct resection (EBDR)[16,17] Such an approach eradicates the entire biliary tree with its lymphatic drainage and complies with the basic oncosurgical objective of achieving wide safety margins while avoiding dissection in tumour-bearing areas. Five-year survival rates up to 65% have been achieved by hilar en bloc resection in selected patients.[17,18] Seehofer et al[17] compared patients undergoing EBDR with those who had LT and found encouraging results in lymph node–negative patients. The 10-year survival of 14 patients without lymph node and distant metastases (UICC stages I and IIA) was 56%, including perioperative mortality in both those undergoing EBDR (n = 11) or LT alone (n = 3). However, EBDR was associated with much higher perioperative mortality. Hence the investigators do not recommended EBDR over LT alone. Taken together these studies appear to favour LT over more radical resections.

Liver transplantation (LT)

The rationale for LT in cholangiocarcinoma has been discussed by Pandey et al.[19] Although surgical resection is the treatment of choice, there exists a subgroup of unresectable patients in whom there is no evidence of tumour spread. In these cases, a possible alternative to palliative treatment is LT. LT theoretically provides the opportunity for wide resection margins, thereby increasing the number of patients eligible for surgical intervention.

LT is now part of the treatment regime for conditions like chronic liver disease, primary biliary cirrhosis and also in malignant diseases like hepatocellular carcinoma (HCC) where 10-year overall survival rates exceeding 70% have been confirmed worldwide.[20]

Early experiences with LT for CCA were disappointing and led to many centres abandoning LT altogether. However, many of the earlier studies published before 2000 used less stringent selection criteria and LTs were often done for patients as a last resort when the disease was in an advanced stage (i.e., multicentric bilobar tumours or solitary tumours of a large size)[21] and extrahepatic disease may have been present though undetected by the technologies used at the time. We therefore compared data from studies published prior to 2000 with those since 2000 to determine whether improved patient selection and technology might have resulted in a change in survival figures.

Before 2000

Studies published prior to 2000 showed 5-year survival rate ranging from 0% to 38% for patients with known CCA prior to surgery (Table 1). Early experience obtained by the King's College Hospital/Cambridge Group showed 1-, 3-, and 5- year survival rates for hilar CCA and peripheral CCA of 30.7%, 10%, 10% and 38.4%, 10%, 10%, respectively.[22] Other studies have reported similarly poor figures[23] with early recurrence, most commonly in the peritoneum or head of pancreas.[22] In the European Liver Transplant Registry (ELTR) database, none of the 38 patients with hilar CCA survived 5 years after LT.[24] Another series from Hannover reported a poor 5-year survival rate of 17.1%.[21] Iwatsuki et al from Pittsburgh reported a modest 36.2% 5 year survival for patients undergoing transplantation.[14] Against this scenario many transplant centres have abandoned LT altogether and CCA has even been considered an absolute contraindication for transplantation.[22,23,25]

Since 2000

Five-year survival rates ranged from 0 – 83% according to studies published since 2000 (Table 2). The largest series of patients with CCA came from the ELTR database and comprised 230 with intrahepatic CCA and 226 with extrahepatic CCA. 1-, 3-, 5- year survival rates were similar - 58%, 38%, 29%, and 63%, 38%, 29%, respectively.[26] The second largest series of CCA, reported by the Cincinnati Transplant Tumor Registry database, included 207 patients who underwent LT for otherwise unresectable CCA.[27] The 1-, 2-, and 5- year survival estimates were 72%, 48%, and

23%. Fifty-one percent of patients had recurrence of their tumours after transplantation, 84% of which occurred within 2 years of transplantation. Forty-seven percent of recurrences occurred in the allograft and 30% in the lungs. Survival after recurrence was less than 1 year. Shimoda et al reported on 25 patients with CCA and observed acturial patient survival rates of 71% after 1 year and 35% after 3 years.[28] Weimann et al[29] reported the summarized experience of the Medizinische Hochschule Hannover, Germany, with 24 patients suffering from unresectable CCA prior to LT. Survival rates at 1-, 2-, and 5- years were 21%, 8%, and 0% for patients undergoing LT compared with 64%, 43%, and 21% in patients with who underwent resection.

In our analysis, 5-year survival ranged from 0% to 38% for studies published before 2000 and 0 – 83% for studies published since 2000. The best 5-year survival prior to 2000 was 38% and this was in patients who underwent a pancreaticoduodenectomy (PD) in addition to LT.[18] Among the studies published since 2000, the best 5-year survival figures ranged from 76 - 83% and this was in a highly selected group of patients given neoadjuvant therapy before LT.[3,5,30,31] Three of these studies represented preliminary and updated reports from one centre - the Mayo Clinic which used neoadjuvant chemoradiation before LT.[3,5,30] The other study came from the University of Arkansas which used neoadjuvant radiotherapy (external-beam and brachytherapy without chemotherapy) therapy.[31] This study was small consisting of only 6 patients with early-stage CCA complicating PSC and involved en bloc total hepatectomy–pancreaticoduodenectomy–liver transplantation (LT-Whipple) to achieve complete eradication. If all these four studies were excluded, 5-year survival would range from 0 – 45%, which is not much different from the 0 - 38% seen in pre-2000 studies. It would appear therefore, that neoadjuvant chemoradiation as used by the Mayo Clinic and neoadjuvant radiotherapy as used by the University of Arkansas were largely responsible for the improvement in 5-year survival rates seen in studies published since 2000.

In an earlier study based on registry data, Becker et al[32] analysed the outcome of 280 patients with CCA treated with orthotopic LT from the United Network for Organ Sharing (UNOS) database and observed no survival improvement between data from 1994–2000 and 2001–2005. The 66 patients transplanted from 1994–2000 experienced a 3-year survival rate of 58% and the median survival time was 1,367 days. The 3-year and median survivals for the 113 patients transplanted from 2001–2005 were 60% and 1,242 days, respectively (p=0.569).

A few studies have suggested that survival is better when the CCA is found incidentally in the explanted liver of patients transplanted for PSC compared to known malignancy prior to transplant.[33,34] However this has not borne out by several other studies.[5,27,35,36] A retrospective national Canadian analysis of outcomes found that even though the tumours tend to be early-stage and short-term survival appeared to be quite good, survival at 3 years after transplant was no better than that for known CCA.[35] The tumour recurrence rate was 80% within a median of 26 months post-transplant, producing a 3-year survival of 30%. Becker et al[32] analysed the outcome of 280 patients with CCA treated with LT from 1987 to 2005 from the UNOS database. The 5-year survival rate for patients with known CCA was 68%, and the median survival time was not reached. In contrast, patients with incidental CCA found in the explanted liver experienced 5-year survivals of only 20%, with a median survival time of only 640 days ($p<0.001$). A number of reasons have been proposed. Firstly, patients with known CCA are likely to undergo additional staging studies to confirm the absence of metastases prior to LT listing (i.e., selection bias). Secondly, patients with incidental CCA may harbor undetected distant disease, a more advance stage at the time of transplant, and consequently, a poorer prognosis.

From the cumulative experience with LT for hilar CCA, it is clear that long-term survival in a significant proportion of patients is achievable only in nodal-negative patients. This was demonstrated first by groups from Pittsburgh[37] and Hannover[21] and confirmed by others.[14,17] The Hannover group reported a 3- and 5-year survival of 56% and 44%, respectively, in lymph node–negative patients, whereas no patient with positive lymph nodes survived longer than 16 months.

Extended LT

In an effort to negate locoregional recurrence and improve CCA results, the strategy evolved to widen the area of resection by exenteration of the upper abdomen including resection of the liver, stomach, spleen, pancreas duodenum, and part of the colon, followed by abdominal organ cluster transplantation.[16, 37, 38] Modest survival rates of 50%, 25% and 20% at 1, 2 and 3 years respectively were observed among 20 CCA patients leading the investigators to conclude that unless the disease had advanced beyond the liver and bile ducts the procedure was unlikely to be of any additional benefit.[16,37] LT has also been combined with pancreatoduodenectomy[18,40] and EBDR.[39] Neuhaus et al[18] described the results of LT and partial pancreatectomy (LTPP) as a so-called “no-touch

technique" for the resection of hilar CCA. Although 14 of the 15 patients who underwent LTPP had R0 resection, the 5-year survival was a modest 38%. EBDR followed by LT achieved curative resection in 93% of cases, as compared with 70% of their patients who underwent partial hepatic resection. However the 14 patients who underwent EDBR in addition to their LT achieved a 29.8% 4 year survival which is not much better that that observed with LT alone.[39] Iwatsuki et al from Pittsburgh reported a 5-year survival of 36.2% for patients undergoing transplantation vs. 9.1% for those undergoing more aggressive cluster abdominal transplantation.[14] These results suggest that extended resections should be reserved for patients with a positive frozen section examination of the bile duct margin, as practised in the Mayo Clinic protocol.[5]

LT with adjuvant radiation or chemotherapy

A few studies have reported increased survival rates after adjuvant radiation therapy in surgically resected patients with CCA.[39-41] These studies were retrospective and there may have been selection bias in favour of patients receiving adjuvant radiation. Pitt et al designed a prospective, randomized study of patients with hilar CCA and observed that only resection could improve survival, while post-operative radiotherapy failed to improve survival or quality of life in these patients.[42]

Chemotherapy has not been shown to improve survival in patients with either resected or unresected hilar CCA.[43] A recently published multi-institutional phase III study, which compared postoperative chemotherapy with resection alone, found no significant difference in 5-year survival rates between patients who received chemotherapy and surgery and those who received surgery alone following either margin-negative or margin-positive resection.[44]

The era of neo-adjuvant chemoradiation

In 2000, a group from Mayo Clinic presented their preliminary result of their protocol of neoadjuvant chemoradiation followed by LT in 11 patients with hilar CCA.[45] All 11 patients were alive and only one had recurrent disease at the time of publication of the article. Three patients had less than 1 year of follow-up while the other patients had a follow-up of 17 to 83 months. Subsequently another group, this time from the University of Nebraska[46] used a similar protocol of neoadjuvant biliary brachytherapy at 6000 cGy and 5-fluorouracil chemotherapy without the external beam radiotherapy. At a median follow-up of 7.5 years, 5 (45%) of 11 patients with stage III CCA were alive without evidence of tumour recurrence. However the treatment was accompanied by a relatively high rate of mainly septic complications preoperatively and postoperatively which may be related to the higher dose of brachytherapy (6000 cGy) compared to the 2000-3000 cGY dose used by the Mayo group.

In the updated series from the Mayo Clinic, 71 patients have entered the transplant treatment protocol and received chemoradiation.[5] Eventually, 38 patients underwent LT and 3 died of surgical complications. Patient survivals at 1, 3, and 5 years after transplantation were 92%, 82%, and 82%, respectively. These were superior to the non-transplanted group (*vide infra*). One-, 3-, and 5-year recurrence rates following transplantation were 0%, 5%, and 12% respectively. The Mayo Clinic protocol comprised of neoadjuvant brachytherapy at a target dose of 2000-3000 cGy, external beam radiation at 4500 cGy and chemotherapy (oral capecitabine, 2 g/day for 2 of every 3 weeks until transplantation) applied in combination with strict patient selection. This patient selection was ensured by a mandatory staging laparotomy after completion of neoadjuvant therapy with complete abdominal exploration and routine biopsy of regional lymph nodes, and it "is a major reason for the success of the Mayo Clinic treatment protocol."[30] According to the latest update from the Mayo Clinic, 65 patients have undergone transplants and 1- and 5-year survivals were 91 and 76%, respectively, with a median follow up interval of 18 months.[36]

Neoadjuvant PDT

Photodynamic therapy (PDT) involves the systemic administration of a photosensitizer such as a haematoporphyrin derivative that accumulates specifically in malignant cells followed by endoscopic application of red laser light. The activated photosensitizer forms cytotoxic reaction products, including singlet oxygen radicals that destroy cancer and neovascular cells and induce tumour thrombosis. PDT has been used successfully in the palliative management of patients with hilar CCA.[47,48] The authors reported that the median survival time of the patients was prolonged compared to that in other published reports and noted improvement in biliary drainage and quality of life. One patient with hilar CCA showed complete destruction of the tumour, which was confined to the superficial 4 mm of the bile duct.[48] Wiedmann et al[49] reported a phase II study of PDT for advanced hilar CCA. One of the seven patients received a combined LT and PD for an advanced Bismuth-Corlette type IV tumour with regional lymph node involvement, whereas the other patients were treated

by combined hilar resection and partial hepatectomy. After a median follow-up of 16 months, two patients had died of recurrent disease, whereas the other patients were alive without evidence of tumour. The patient treated by LT and PD was alive and tumour-free 40 months after transplantation.[49] This suggests that neoadjuvant PDT might have potential in the treatment of hilar CCA.

Living donor liver transplantation (LDLT)

There has been resurgence of interest in LT for CCA following the publication of impressive survival data from the Mayo Clinic in patients treated with neoadjuvant chemoradiation.[5] In a carefully selected group of patients with hilar CCA, the 5-year survival is as good as that observed, for example, in patients transplanted for hepatocellular carcinoma within the Milan criteria.[20] Unfortunately, the waiting list for cadaveric organs, including livers is extremely long and patients with CCA are unlikely to survive long enough to benefit from deceased donor liver transplantation (DDLT). Axelrod et al from Pittsburgh reported on the results of living donor grafts in 5 patients with CCA, all of whom had PSC.[50] Four of the five received concurrent chemotherapy and radiation prior to transplantation and were recurrence free at a mean follow up of 18 months.

The impressive survival figures from the Mayo Clinic suggest that neoadjuvant chemoradiation and LT has a place in the management of a highly selected group of patients with hilar CCA. Concern has generally been expressed that DDLT in patients with malignant disease would penalize other patients on the waiting list with non-malignant liver disease. This question does not arise in the case of LDLT. Hence, LDLT may be an option, especially in Asian countries where the deceased donor rates range from 0.07 – 6.5 deceased donors per million of population among the Asian transplantation centres compared to those of Western countries (35.1 per million population in Spain and 25.2 per million population in the US).[51,52]

Conclusion

CCA is an aggressive disease with a poor prognosis. Surgical resection, the treatment of choice may not be an option because of tumour extension, parenchymal liver disease or tumour location. LT is an alternative to palliative treatment in these patients although there is a possibility of immunosuppression accelerating the progression of unidentified tumour remains.[14,27]

Early results with LT were disappointing. However, recent and impressive 5-year survival figures from the Mayo Clinic[3,5,30] in particular suggests that neoadjuvant chemoradiation prior to LT is worth considering. Neoadjuvant radiotherapy (without chemotherapy) prior to LT as practised by Wu et al[31] from the University of Arkansas may have potential but needs to evaluated in a larger number of patients. Furthermore, all these reports have been emanated from single centres and require confirmation in multi-centre studies.

It is important to note that the Mayo Clinic protocol puts patients through stringent staging laparotomies and only those who responded went on to receive LT. Hence, it can be argued that only those with good tumour biology were selected and this might account for the subsequent increase in survival. Accordingly, it is hoped that molecular testing can better define tumour biology in the near future and aid in the selection of cases for LT.

Additionally, despite the encouraging survival figures, the Mayo Clinic protocol is not without problems. LT with neoadjuvant radiotherapy and chemosensitization is associated with higher rates of late hepatic artery and portal venous complications than is LT without neoadjuvant therapy.[53] The adverse effect of radiotherapy on vascular tissue is well known. Vascular endothelial cells are quite radiosensitive, and smaller vessels are especially sensitive to radiation injury.[54] PDT has shown promise in the palliative treatment of hilar CCA[48] and encouraging survival figures have been reported with the use of neoadjuvant PDT in a few patients undergoing resection and in a single patient undergoing LT and PD for hilar CCA.[49] It would also be very interesting to see more studies combining neoadjuvant PDT, which is less likely to cause vascular damage, with LT.

With 5-year survival in excess of 70% in a highly selected patients with CCA, it may no longer be justifiable to categorically deny these patients LT. LDLT does not penalize patients other patients on the waiting list with non-malignant liver disease and can be considered as an alternative.

High tumour recurrence rates is the norm after liver transplantation.[14,27,55] and there have been concerns that the immunosuppressive drugs used after LT may actually accelerate the progression of unidentified tumour remains.[14,27] The discovery of new immunosuppressive agents with antiproliferative effects is a welcomed advance. Sirolimus (Rapamycin) has been shown in in-vitro studies on hepatoma cell lines to suppress cell proliferation, whereas calcineurin inhibitors promoted it.[56] It also inhibited the

growth of lung metastases in mice injected with murine colon cancer cells whereas cyclosporin promoted it.[57] Decreased tumour growth and tumour vascularization was observed in sirolimus treated mice, whereas early neovascularization and accelerated tumour growth were seen with cyclosporin.[57] Kneteman et al[58] reported an excellent outcome in patients who were treated with a sirolimus-based immunosuppression regimen after LT for hepatocellular carcinoma. Twenty-one of the 40 patients in their series had tumour stages beyond the Milan criteria. The 1- and 4-year survival of the patients with extended tumour stages was 90.5% and 82.9%, respectively, which was comparable to patients with tumours within the Milan criteria

Directed biological therapy targeting epidermal growth factor-receptor (EGF-R) is another promising area since it now seems apparent aberrant EGF-R and/or ErbB2 expression and signaling is associated with the molecular pathogenesis of intrahepatic cholangiocarcinoma.[59]

References

1. Khan SA, Davidson BR, Goldin R, Pereira SP, Rosenberg WM, Taylor-Robinson SD, Thillainayagam AV, Thomas HC, Thursz MR, Wasan H. Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document. Gut 2002; 51(Suppl 6): 1–9.
2. Reddy BR, Patel T. Current approaches to the diagnosis and treatment of cholangiocarcinoma. Current Gastroenterology Reports 2006; 8 (1): 30-37.
3. Heimbach JK, Haddock MG, Alberts SR, Nyberg SL, Ishitani MB, Rosen CB, Gores GJ. Transplantation For Hilar Cholangiocarcinoma. Liver Transplantation 2004; 10 (Suppl 2): S65–S68.
4. Seehofer D, Kamphues C, Neuhaus P: Management of bile duct tumors. Expert Opin Pharmacother 2008; 9(16): 2843-2856.
5. Rea DJ, Heimbach JK, Rosen CB, Haddock MG, Alberts SR, Kremers WK, Gores GJ, Nagorney DM. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. Ann Surg 2005; 242(3): 451-461.
6. Sandhu DS, Roberts LR. Diagnosis and management of cholangiocarcinoma. Curr gastro reports 2008; 10(1): 43-52.
7. Eckel F, Schmid RM. Chemotherapy in advanced biliary tract carcinoma:A pooled analysis of clinical trials. Br J Cancer 2007; 96(6): 896 –902.
8. Lindner P, Norrby J, Olausson M, Friman S. Survival after liver transplantation for cholangiocarcinoma has increased during the last decade. Transpl Proc 2003; 35(2) :811-812.
9. Jarnagin WR. Cholangiocarcinoma of the extrahepatic bile ducts. Semin Surg Oncol 2000; 19(2): 156–176.
10. Lillemoe KD, Cameron JL. Surgery for hilar cholangiocarcinoma: the Johns Hopkins approach. J Hepatobiliary Pancreat Surg 2000; 7(2): 115-121.
11. Havlik R, Sbisa E, Tullo A, Kelly MD, Mitry RR, Jiao LR, Mansour MR, Honda K, Habib NA. Results of resection for hilar cholangiocarcinoma with analysis of prognostic factors. Hepatogastroenterology 2000; 47(34): 927-931.
12. Nimura Y, Kamiya J, Kondo S, Nagino M, Uesaka K, Oda K, Sano T, Yamamoto H, Hayakawa N. Aggressive preoperative management and extended surgery for hilar cholangiocarcinoma: Nagoya experience. J Hepatobiliary Pancreat Surg 2000; 7(2): 155-162.
13. Kondo S, Hirano S, Ambo Y, Tanaka E, Okushiba S, Morikawa T, Katoh H. Resections of Hilar Cholangiocarcinoma With No Postoperative Mortality and No Positive Ductal Margins: Results of a Prospective Study. Ann Surg 2004; 240(1): 95-101.
14. Iwatsuki S, Todo S, Marsh JW, Madariaga JR, Lee RG, Dvorchik I, Fung JJ, Starzl TE. Treatment of hilar cholangiocarcinoma (Klatskin tumors) with hepatic resection or transplantation. J Am Coll Surg 1998; 187(4): 358–364.
15. Launois B, Jamieson GG. Pylorus-preserving 'cluster' operation. Br J Surg 1991; 78(8): 1015.
16. Neuhaus P, Blumhardt G. Extended bile duct resection—a new oncological approach to the treatment of central bile duct carcinomas? Description of method and early results. Langenbecks Arch Chir 1994; 379(2): 123-128.
17. Seehofer, Thelen A, Neumann UP, Veltzke-Schlieker W, Denecke T, Kamphues C, Pratschke J, Jonas S, Neuhaus P. Extended Bile Duct Resection Liver and Transplantation in Patients with Hilar Cholangiocarcinoma: Long-Term Results. Liver Transplantation 2009; 15(11): 1499-1507.
18. Neuhaus P, Jonas S, Bechstein WO, Lohmann R, Radke C, Kling N, Wex C , Lobeck H,, Hintze R. Extended resections for hilar cholangiocarcinoma. Ann Surg 1999; 230(6): 808-819.
19. Pandey D, Lee KH, Tan KC. The Role of Liver Transplantation for Hilar Cholangiocarcinoma Hepatobiliary Pancreat Dis Int 2007; 6(3): 248 253.
20. Bruix J, Fuster J, Llovet JM. Liver transplantation for hepatocellular carcinoma: Foucault pendulum versus evidence based decision. Liver Transpl 2003; 9(7): 700–702.
21. Pichlmayr R, Weimann A, Klempnauer J, Oldhafer KJ, Maschek H, Tusch G, Ringe B. Surgical treatment in proximal bile duct cancer. A single-center experience. Annals of Surgery 1996; 224(5): 628-638.
22. O'Grady JG, Polson RJ, Rolles K, Calne RY, Williams R. Liver transplantation for malignant disease. Ann Surg 1988; 207(4): 373–379.
23. Ringe B, Wittekind C, Bechstein WO, Bunzendahl H, Pichlmayr R. The role of liver transplantation in hepatobiliary malignancy. A retrospective analysis of 95 patients with particular regard to tumor stage and recurrence. Ann Surg 1989; 209(1): 88-98.

24. Bismuth H, Castaing D, Ericzon BG, Otte JB, Rolles K, Ringe B, Sloof M. Hepatic transplantation in Europe. First report of the European Liver Transplant Registry. Lancet 1987; 2(8560): 674-676.

25. Jeyarajah DR, Klintmalm GB. Is liver transplantation indicated for cholangiocarcinoma? J Hepatobiliary Pancreat Surg 1995; 5(1): 48-51.

26. Pascher A, Jonas S, Neuhaus P. Intrahepatic cholangiocarcinoma: indication for transplantation. J Hepatobiliary Pancreat Surg 2003; 10(4): 282-287.

27. Meyer CG, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. Transplantation 2000; 69(8): 1633-1637.

28. Shimoda M, Farmer DG, Colquhoun SD, Rosove M, Ghobrial RM, Yersiz H, Chen P, Busuttil RW. Liver transplantation for cholangiocellular carcinoma: analysis of a single-center experience and review of the literature. Liver Transpl 2001; 7(12): 1023-1033.

29. Weimann A, Varnholt H, Schlitt HJ, Lang H, Flemming P, Hustedt C, Tusch G, Raab R. Retrospective analysis of prognostic factors after liver resection and transplantation for cholangiocellular carcinoma. Br J Surg 2000; 87(9): 1182-1187.

30. Heimbach J, Gores GJ, Nagorney DM, Rosen CB. Liver transplantation for perihilar cholangiocarcinoma after aggressive neoadjuvant therapy: a new paradigm for liver and biliary malignancies? Surgery 2006; 140(3): 331-334.

31. Wu Y, Johlin FC, Rayhill SC, Jensen CS, Xie J, Cohen MB, Mitros FA. Long-Term, Tumor-Free Survival After Radiotherapy Combining Hepatectomy-Whipple En Bloc and Orthotopic Liver Transplantation for Early-Stage Hilar Cholangiocarcinoma. Liver transplantation 2008; 14(3): 279-286.

32. Becker NS, Rodriguez JL, Barshes NR, O'Mahony CA, Goss JA, Aloia TA. Outcomes analysis for 280 patients with cholangiocarcinoma treated with liver transplantation over an 18-year period. J Gastrointest Surg. 2008; 12(1): 117-122.

33. Goss JA, Shackleton CR, Farmer DG. Orthotopic liver transplantation for primary sclerosing cholangitis. A 12-year single centre experience. Ann Surg 1997; 225(5): 472-481.

34. Broome U, Olsson R, Loof L. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. Gut 1996; 38(4): 610-615.

35. Ghali P, Marotta PJ, Yoshida EM, Bain VG, Marleau D, Peltekian K, Metrakos P, Deschenes M. Liver transplantation for incidental cholangiocarcinoma: analysis of the Canadian experience. Liver Transpl 2005; 11(11): 1412–1416.

36. Heimbach JK, Gores GJ, Haddock MG, Alberts SR, Pedersen R, Kremers W, Nyberg SL, Ishitani MB, Rosen CB. Predictors of disease recurrence following neoadjuvant chemoradiotherapy and liver transplantation for unresectable perihilar cholangiocarcinoma. Transplantation 2006; 82(12): 1703–1707.

37. Alessiani M, Tzakis A, Todo S, Demetris AJ, Fung JJ, Starzl TE. Assessment of five-year experience with abdominal organ cluster transplantation. J Am Coll Surg 1995; 180(1): 1-9.

38. Starzl TE, Todo S, Tzakis A, Podesta L, Mieles L, Demetris A, Teperman L, Selby R, Stevenson W, Stieber A. Abdominal organ cluster transplantation for the treatment of upper abdominal malignancies. Ann Surg 1989; 210(3): 374–386.

39. Jonas S, Kling N, Guckelberger O, Keck H, Bechstein WO, Neuhaus P. Orthotopic liver transplantation after extended bile duct resection as treatment of hilar cholangiocarcinoma. First long-term results. Transpl Int 1998; 11(Suppl 1): S206–S208.

40. Cherqui D, Alon R, Piedbois P, Duvoux C. Dhumeaux D. Julien M. Fagniez PL. Combined liver transplantation and pancreatoduodenectomy for irresectable hilar bile duct carcinoma. Br J Surg 1995; 82(3): 397–398.

41. Cameron JL, Pitt HA, Zinner MJ, Kaufman SL, Coleman J. Management of proximal cholangiocarcinomas by surgical resection and radiotherapy. Am J Surg 1990; 159(1): 91–97.

42. Pitt HA, Nakeeb A, Abrams RA, Coleman J, Piantadosi S, Yeo CJ, Lillemore KD, Cameron J. Perihilar cholangiocarcinoma. Postoperative radiotherapy does not improve survival. Ann Surg 1995; 221(6): 788-797.

43. Todoroki T. Chemotherapy for bile duct carcinoma in the light of adjuvant chemotherapy to surgery. Hepatogastroenterology 2000; 47(33): 639-643.

44. Takada T, Amano H, Yasuda H, Nimura Y, Matsushiro T, Kato H, Nagakawa T, Nakayama T. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. Cancer 2002; 95(8): 1685-1695.

45. De Vreede I, Steers JL, Burch PA, Rosen CB, Gunderson LL, Haddock MG, Burgart L, Gores GJ. Prolonged disease-free survival after orthotopic liver transplantation plus adjuvant chemoirradiation for cholangiocarcinoma. Liver Transpl 2000; 6(3): 309-316.

46. Sudan D, DeRoover A, Chinnakotla S, Fox I, Shaw B Jr, McCashland T, Sorrell M, Tempero M, Langnas A. Radiochemotherapy and transplantation allow long-term survival for nonresectable hilar cholangiocarcinoma. Am J Transplant 2002; 2)8): 774-779.

47. Ortner MA, Liebetrith J, Schreiber S, Hanft M, Wruck U, Fusco V, Muller JM. Hortnagl H. Lochs H. Photodynamic therapy of nonresectable cholangiocarcinoma. Gastroenterology 1998; 114(3): 536-542.

48. Berr F, Wiedmann M, Tannapfel A, Halm U, Kohlhaw KR, Schmidt F, Wittekind C. Hauss J. Mossner J. Photodynamic therapy for advanced bile duct cancer: evidence for improved palliation and extended survival. Hepatology 2000; 31(2) :291-298.

49. Wiedmann M, Caca K, Berr F, Schiefke I, Tannapfel A, Wittekind C, Mossner J. Hauss J. Witzigmann H. Neoadjuvant photodynamic therapy as a new approach to treating hilar cholangiocarcinoma. Cancer 2003; 97(11): 2783-2790.

50. Axelrod D, Koffron A, Kulik L, Al-Saden P, Mulcahy M, Baker T, Fryer, Abecassis M. Living donor liver transplant for malignancy. Transplantation 2005; 79(3): 363-366.

51. de Villa V, Lo CM. Liver transplantation for hepatocellular carcinoma in Asia. Oncologist 2007; 12(11): 1321-1231.

52. Ng KK, Lo CM. Liver Transplantation in Asia: Past, Present and Future. Ann Acad Med Singapore 2009; 38(4): 322-331.

53. Mantel HTJ, Rosen CB, Heimbach JK, Nyberg SL, Ishitani MB, Andrews JC, McKusick MA, Haddock MG, Alberts SR, Gores GJ. Vascular complications after orthotopic liver transplantation after neoadjuvant therapy for hilar cholangiocarcinoma. Liver transplantation 2007; 13(10): 1372-1381.

54. Fajardo LF, Berthrong M. Vascular lesions following radiation. Pathol Annu 1988; 23(Part 1): 297-330

55. Pichlmayr R, Weimann A, Oldhafer KJ, Schlitt HJ, Klempnauer J, Bornscheuer A, Chavan A, Schmoll E, Lang H, Tusch G. Role of liver transplantation in the treatment of unresectable liver cancer. World J Surg 1995; 19(6): 807-813.

56. Schumacher G, Oidtmann M, Rosewicz S, Langrehr J, Jonas S, Mueller AR, Rueggeberg A. Neuhaus R. Bahra M. Jacob D. Gerlach H. Neuhaus P. Sirolimus inhibits growth of human hepatoma cells in contrast to tacrolimus which promotes cell growth. Transplant Proc 2002; 34(5): 1392–1393.

57. Guba M, von Breitenbuch P, Steinbauer M, Koehl G, Flegel S, Hornung M, Bruns CJ. Zuelke C. Farkas S. Anthuber M. Jauch KW. Geissler EK. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. Nat Med 2002; 8(2): 128–135.

58. Kneteman NM, Oberholzer J, Al Saghier M, Meeberg GA, Blitz M, Ma MM, Wong WW, Gutfreund K, Mason AL, Jewell LD, Shapiro AM, Bain VG, Bigam DL. Sirolimus-Based immunosuppression for liver transplantation in the presence of extended criteria for hepatocellular carcinoma. Liver Transpl 2004; 10(10): 1301–1311.

59. Sirica AE. Role of ErbB family receptor tyrosine kinases in intrahepatic cholangiocarcinoma. World J Gastroenterol 2008; 14(46): 7033-7058.

60. Haug CE, Jenkins RL, Rohrer RJ, Auchincloss H. Delmonico FL. Freeman RB. Lewis WD. Cosimi AB. Liver transplantation for primary hepatic cancer. Transplantation 1992; 53(2): 376–382.

61. Calne R, Yamanoi A, Oura S, Kawamura M. Liver Transplantation for Hepatocarcinoma. Surgery Today 1993; 23(1): 1-3.

62. Nashan B, Schlitt HJ, Tusch G, Oldhafer KJ, Ringe B, Wagner S, Pichlmayr R. Biliary malignancies in primary sclerosing cholangitis: timing for liver transplantation. Hepatology 1996; 23(5): 1105-1111.

63. Casavilla FA, Marsh JW, Iwatsuki S,Todo S, Lee RG, Madariaga JR, Pinna A. Dvorchik I. Fung JJ. Starzl TE. Hepatic resection and transplantation for peripheral cholangiocarcinoma. J Am Coll Surg 1997; 185(5): 429-436.

64. Chung SW, Greig PD, Cattral MS, Taylor BR, Sheiner PA, Wanless I, Cameron R, Phillips MJ, Blendis LM, Langer B, Levy GA. Evaluation of liver transplantation for high-risk indications. Br J Surg 1997; 84(2): 189-195.

65. Robles R, Parrilla P, Bueno F S, Ramirez P, Lujan J A, Rodriguez J M, Acosta F, Lopez J, Hernandez Q. Liver Transplantation in the management of Klastkin's Tumor. Transplantation Proceedings 1999; 31(6): 2494-2495.

66. Bismuth H. Revisiting liver transplantation for patients with hilar cholangiocarcinoma: the Mayo Clinic proposal. Liver Transplantation 2000; 6(3): 317-319.

67. Robles R, Figueras J, Turrion VS, Margarit C, Moya A, Varo E, Calleja J, Valdivieso A, Garcia-Valdelcasas JC, Lopez P, Gomez M, de Vicente E, Loinaz C, Santoyo J, Fleiras M, Bernardos A, Marin C, Fernandez JA, Jaurrieta E, Parrilla P. Liver transplantation for peripheral cholangiocarcinoma: Spanish experience. Transplantation Proceedings 2003; 35(5): 1823-1824.

68. Robles R, Figueras J, Turrion VS, Margarit C. Moya A. Varo E. Calleja J. Valdivieso A. Valdecasas JC. Lopez P. Gomez M. de Vicente E. Loinaz C. Santoyo J. Fleitas M. Bernardos A. Llado L. Ramirez P. Bueno FS. Jaurrieta E. Parrilla P. Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma. Ann Surg 2004; 239(2): 265-271.

69. Jonas S, Mittler J, Pascher A, Theruvath T. Thelen A. Klupp J. Langrehr JM. Neuhaus P. Extended indications in living-donor liver transplantation: bile duct cancer. Transplantation 2005; 80(Suppl 1): S101-S104.

70. Robles R, Marin C, Pastor P, Ramirez P, Sanchez-Bueno F, Pons JA, Parrilla P. Liver transplantation for Klatskin's tumor: contraindicated, palliative, or indicated? Transplantation Proceedings 2007; 39(7): 2293-2294.

71. Sotiropoulos GC. Kaiser GM. Lang H. Molmenti EP. Beckebaum S. Fouzas I. Sgourakis G. Radtke A. Bockhorn M. Nadalin S. Treckmann J. Niebel W. Baba HA. Broelsch CE. Paul A. Liver Transplantation as a Primary Indication for Intrahepatic Cholangiocarcinoma: A Single-Center Experience. Transplantation Proceedings 2008; 40(9): 3194-3195.

72. Kaiser GM. Sotiropoulos GC. Jauch KW. Lohe F. Hirner A. Kalff JC. Konigsrainer A. Steurer W. Senninger N. Brockmann JG. Schlitt HJ. Zulke C. Buchler MW. Schemmer P. Settmacher U. Hauss J. Lippert H. Hopt UT. Otto G. Heiss MM. Bechstein WO. Timm S. Klar E. Holscher AH. Rogiers X. Stangl M. Hohenberger W. Muller V. Molmenti EP. Fouzas I. Erhard J. Malago M. Paul A. Broelsch CE. Lang H. Liver transplantation for hilar cholangiocarcinoma: a German survey. Transplantation Proceedings. 2008; 40(9): 3191-3193.

Table 1. Studies prior to 2000

Reference	Centre	No.	Type of CCA	Additional Procedure	Patient Survival (%)				
					1yr	2yr	3yr	4yr	5yr
O'Grady[22] (1988)	Kings College Hospital, London, UK	13	Hilar CCA		30.7		10		10
		13	Intrahepatic CCA		38.4		10		10
Ringe[23] (1989)	Hannover, Germany	10	Intrahepatic CCA		10	10			
		20	Hilar CCA		55	40			
Haug[60] (1992)	Boston Centre for Liver Transplantation	9	CCA*		56	56	56		
Calne[61] (1993)	Cambridge/Kings Hospital, London	13	CCA†						23.8
Pichlmayr[55] (1995)	Hannover, Germany (1972-1994)	22	Intrahepatic CCA		20.8		0		
Pichlmayr[21] (1996)	Hannover, Germany (1973-1993)	25	Hilar CCA		60		21.4		17.1
Nashan[62] (1996)	Hannover, Germany	10	CCA†		30		10		10
Casavilla[63] (1997)	University of Pittsburgh Medical Centre, Pittsburgh, US	20	Intrahepatic CCA	Chemotherapy or Radiotherapy before or after LT	70		29		18
Chung[64] (1997)	Toronto, Canada	6	CCA		83	21	21		
Iwatsuki[14] (1998)	University of Pittsburgh Medical Centre, Pittsburgh, US	27	Hilar CCA	Radiotherapy +/- Chemotherapy before or after LT	59.3	40.7	36.2	36.2	36.2
Jonas [39] (1998)	Berlin, Germany	14	Hilar CCA	EBDR	55.9			29.8	
Jeyarajah[25] (1998)	Baylor University, Dallas, Texas	17	CCA	Adjuvant Chemotherapy with radiotherapy	53%		41		
Robles[65] (1999)	Virgen de la Arrixaca University Hospital, Murcia, Spain	6	Hilar CCA		83.3		66.7		
Neuhaus[18] (1999)	Berlin, Germany	11	Hilar CCA	PD					38

*Type not specified
†Consist of both Extrahepatic and Intrahepatic types

Table 2. Studies since 2000

Reference	Centre	No.	Type of CCA	Additional Procedure	Patient Survival (%)				
					1yr	2yr	3yr	4yr	5yr
Weimann[29] (2000)	Hannover, Germany	24	Intrahepatic CCA	+/- Adjuvant chemotherapy	21	8	4		0
De Vreede[45] (2000)	Mayo Clinic, Rochester	11	Hilar CCA	Neoadjuvant Chemotherapy and Radiotherapy	100				
Meyer[27] (2000)	Cincinnati Transplant Tumour Register	207	CCA†	Chemotherapy and Radiotherapy before or after LT	72	48			23
Bismuth[66] (2000)	Paris, France	9	Hilar CCA				33.3		
Shimoda[28] (2001)	UCLA, California	25	Total	+/- Adjuvant chemotherapy	71		35		
		16	Intrahepatic CCA		62		39		
		9	Hilar CCA		86		31		
Sudan[46] (2002)	University of Nebraska	11	Hilar CCA	Neoadjuvant Chemotherapy and Radiotherapy					45
Pascher[26] (2002)	ELTR	186	Intrahepatic CCA		58		38		29
		169	Hilar CCA		63		38		29
Robles[67] (2003)	Spain (multicentre) (1988-2001)	23	Intrahepatic CCA		77		65		42
Linder[8] (2003)	Sahlgrenska University Hospital, Goteborg, Sweden	15	CCA†				33		
Robles[68] (2004)	Spain (multicentre) (1988-2001)	36	Hilar CCA		82		53		30
Heimbach[3] (2004)	Mayo Clinic, Rochester	28	Hilar CCA	Neoadjuvant Chemotherapy and Radiotherapy	88				82
Axelrod[50] (2005)	Northwestern University, Chicago	5	CCA*	Neoadjuvant chemotherapy and Radiotherapy	100				

Rea[5] (2005)	Mayo Clinic, Rochester	38	Hilar CCA	Neoadjuvant chemotherapy and Radiotherapy 4 had PD	92		82		82
Jonas[69] (2005)	Berlin, Germany	7	CCA†		85.7				
Ghali[35] (2005)	Canada (Multicentre)	10	CCA†				30		
Heimbach[36] (2006)	Mayo Clinic, Rochester	65	65 HCC	Neoadjuvant chemotherapy and Radiotherapy	91				76
Robles[70] (2007)	Murcia, Spain (1988-2006)	10	Hilar CCA		80		60		37
Sotiropoulos[71] (2008)	Berlin, Germany	10	10 patients		70		50		33
Becker[32] (2008)	UNOS database	280	280		74				38
Kaiser[72] (2008)	Germany (Multicentre)	47	Hilar CCA		61		31		22
			Excluding erioperative mortality		85		42		31
Seehofer[17] (2009)	Berlin, Germany	16	Hilar CCA	EBDR	63				38
Wu[31] (2008)	University of Arkansas	6	6	Neoadjuvant Radiotherapy plus Whipples procedure	100	100	100	100	83

*Type not specified
†Consist of both Extrahepatic and Intrahepatic types