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Liver transplantation for hilar cholangiocarcinoma

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Abstract
Hilar cholangiocarcinoma was accepted as an indication for liver transplantation at the beginning of the transplantation era. Owing to disappointing long-term results for this indication, and in parallel, encouraging results in patients with benign disease, hilar cholangiocarcinoma has generally not been accepted as an indication for liver transplantation in recent years. To improve results, more aggressive approaches have been used: "abdominal organ cluster transplantation" and "extended bile duct resection", which lead to increased long-term survival rates. However, with improving results after conventional extrahepatic bile duct resection in combination with partial hepatectomy, extended procedures in combination with liver transplantation never became a real option in the treatment of hilar cholangiocarcinoma. However, new awareness of liver transplantation in the treatment of this cancer has been raised for patients with hilar cholangiocarcinoma in the context of underlying liver diseases such as primary sclerosing cholangitis, which preclude liver resection. Current results show increased survival figures, in particular in well-selected patients with early tumor stages. Further improvements in long-term survival may be reached with new adjuvant and neoadjuvant protocols. Patients with neoadjuvant radiochemotherapy show long-term results similar to those for liver transplantation for other indications. Also, photodynamic therapy and the use of new antiproliferative immunosuppressive agents may be an approach for further improvement of the long-term results. Currently, liver transplantation for the treatment of hilar cholangiocarcinoma should be restricted to centers with experience in the treatment of this cancer and should be taken into consideration in patients with contraindications to liver resection.

Key words Hilar cholangiocarcinoma · Liver transplantation

Introduction

Hilar cholangiocarcinoma was thought to be an ideal indication for liver transplantation in the early days of the transplantation era. As the lesion remains localized in the liver hilum until late in the course of the disease, it was thought to be removed completely by extrahepatic bile duct resection combined with total hepatectomy and replacement of a cadaveric homograft. Actually, in palliatively or nontreated patients a curative resection could be achieved in most cases by liver transplantation.[1,2] In parallel to these encouraging oncological-surgical results, the perioperative outcome in this group of transplant candidates was not inferior to that in patients receiving liver transplantation for other indications, for malignant as well as benign liver diseases.[1,2] But, in contrast to the encouraging early results, the long-term survival was disappointing not only compared to that in patients with benign liver diseases but also compared to that in patients with liver cancer.[1–3] Tumor recurrence was the most common reason for death after successful liver transplantation. Iwatsuki et al.[1] reported recurrence in four of five successfully transplanted patients, and no patient was living 2 years postoperatively. Other authors reported similar results, with high rates of local tumor recurrence and only a small minority of patients surviving for more than 2 years.[1–3] In parallel to the high rate of tumor recurrence, the long-term survival was disappointing, even for early stages of the disease.[1,2,4] Owing to these disappointing results, and in parallel, the encouraging results in patients with benign diseases and hepatocellular carcinoma, the increasing donor organ shortage has led to allocation to those who have the best chance of long-term survival and rehabilitation.

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Extended liver transplantation procedures

As total hepatectomy and liver transplantation have failed to produce favorable results in the treatment of hilar cholangiocarcinoma over the long term, new surgical approaches have been introduced to improve survival. The experiences with adenocarcinoma of the biliary tract have revealed that this tumor principally behaves like other gastrointestinal carcinomas. Therefore, tumor type (nodular or infiltrating), depth of invasion, infiltration of serosa and adjacent tissues (portal vein, hepatic artery) are features that are just as important as hematogenous metastasis to the periphery of the liver. However, while hilar cholangiocarcinomas do not seem to metastasize as early and as frequently as other gastrointestinal cancers, perineural invasion and lymphangiosis carcinomatosa, which can extend up to 2 cm from the tumor into the liver and distally into the hepatoduodenal ligament, were frequently described after the resection of hilar cholangiocarcinomas.[4–9] These typical features of the tumor and the anatomical location at the liver hilum, where the bile duct bifurcation comes into close contact with the right hepatic artery and the portal vein, were responsible for the high rate of microscopic infiltration beyond its visible and palpable extensions.[4,10,11] When total hepatectomy and liver transplantation offer the option to achieve wide tumor-free margins at the proximal border of the tumor, the distal resection line is still close to the tumor. Actually, besides local peritoneal carcinomatosis, the head of the pancreas was very often involved when there was tumor recurrence.[4,12]

Considering these findings and the basic principles of oncological surgery, that removal of the tumor should be performed without close dissection and with at least 1 cm of tumor-free margin, and also considering the embryology, with the liver and the pancreas having an embryological origin in common from the ventral and dorsal diverticula of the foregut that later becomes the duodenum,[13] Starzl et al.[14] introduced "abdominal organ cluster transplantation" for the treatment of hilar cholangiocarcinoma. In this procedure the liver, nearly all of the stomach, spleen, pancreas, duodenum, proximal jejunum, terminal ileum, and ascending and transverse colon were excised. The retrohepatic vena cava was removed with the specimen. The void in the upper abdomen was filled with a composite graft of the liver, pancreas, and duodenum, plus small segments of the proximal jejunum.[14] Despite the extent of the procedure, the perioperative outcome in these patients was encouraging.[14] However, although the procedure provided wide resection margins, tumor recurrence was frequent and long-term survival was achieved in only a minority of the patients.[15]

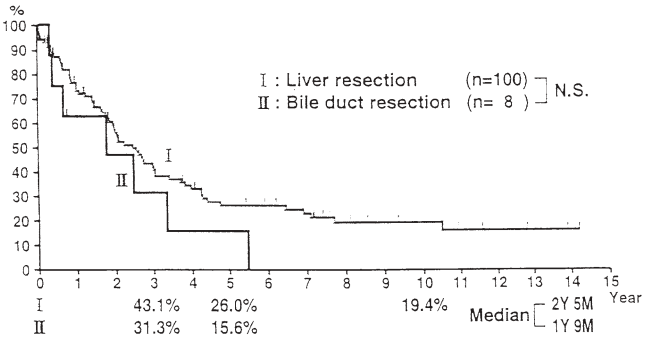


Fig. 1. The Nagoya experience. Cumulative survival of patients with hilar cholangiocarcinoma after extrahepatic bile duct resection ($n = 8$) and combined extrahepatic bile duct resection and hepatectomy ($n = 100$)[19]. *N.S.*, not significant; *Y*, years; *M*, months

Based on the biological behavior of hilar cholangiocarcinoma and the rationale of the surgical oncological principle of wide resection margins and the avoidance of dissection across tumorous tissue, our group developed another approach. The procedure, termed "extended bile duct resection", basically combined total hepatectomy and liver transplantation with a Kausch-Whipple operation.[16] The surgical radicality of the procedure was excellent, with a curative resection in 13 of 14 operated patients (93%). The perioperative mortality was moderate (14%). But, as in Starzl's series of clusters, the majority of the patients in this cohort had advanced tumor stages, despite careful preoperative patient selection. This reveals the difficulty of preoperative evaluation of the tumor extent by the available diagnostic tools. Eight of our 14 patients treated with extended bile duct resection developed tumor recurrence, mostly local peritoneal carcinomatosis. Compared to the long-term survival rates after liver transplantation alone, the long-term survival rate after this procedure was clearly better, and reached 45% at 3 years after curative resection.[17] However, due to the improving results after conventional combined extrahepatic bile duct resection and partial hepatectomy (Fig. 1),[18–20] neither abdominal organ cluster transplantation nor extended bile duct resection became commonly used surgical approaches in the treatment of hilar cholangiocarcinoma.

Liver transplantation and adjuvant therapy

Neither chemotherapy nor radiation therapy had been studied as adjuvant treatments in patients with liver transplantation for hilar cholangiocarcinoma until the mid-1990s. In surgically resected patients, some studies reported increased survival rates after adjuvant radia-

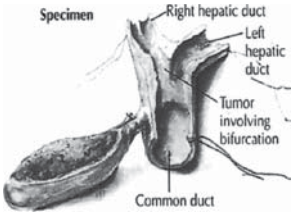
tion therapy.[21–23] However, in all of these retrospective reports, patients receiving radiation therapy tended to have more favorable, often resectable tumors, and were in relatively good general condition. Therefore, the patients with adjuvant radiation therapy had been compared to patients with advanced tumor stages or poor performance status. Thus, the fact that patients receiving radiotherapy in these analyses had survived longer was not surprising. In contrast to these retrospective results, a prospective, randomized study by Pitt et al.,[24] which included patients with comparable characteristics in multiple parameters that may affect the outcome in hilar cholangiocarcinoma, revealed that only resection could improve survival, while radiation failed to improve survival or quality of life in these patients.

Chemotherapy has not been shown to improve survival in patients with either resected or unresected hilar cholangiocarcinoma.[25] In the majority of reports, 5-fluorouracil (FU) was used alone or in combination with methotrexate, leucovorin, cisplatin, mitomycin C, or interferon alpha (IFN-α). The routes of delivery included systemic infusion, hepatic arterial infusion, and intraductal infusion. However, the majority of these reports were small, retrospective, and single-center reviews.[25] A recently published multi-institutional phase III study, which compared postoperative chemotherapy with resection alone, could not reveal any benefit from chemotherapy. The 5-year survival rates were not significantly different between patients who received chemotherapy and surgery and those who received surgery alone following either margin-negative or margin-positive resection.[26]

Hilar cholangiocarcinoma in the context of underlying liver diseases

Using new surgical strategies, the survival rates have been improved markedly. When there was frequent locoregional recurrence after local or hilar resections, including the extrahepatic suprapancreatic biliary tract, even after a formally curative nature of the procedure (Fig. 2),[27,28] long-term survival was achieved in many patients with extrahepatic bile duct resection and major hepatectomy (Fig. 1).[18–20] Furthermore, the perioperative mortality rate has been reduced by approaches that improve hepatocellular function, including decompression of the biliary system and the preoperative induction of hypertrophy of the future remnant liver, induced by unilateral portal vein or arterial embolization.[29,30]

However, many patients with hilar cholangiocarcinoma and additional liver disease are not suitable for major liver surgery, because of insufficient remnant liver function. Multiple liver pathologies are known to be risk factors for the development of cholangiocarcinoma. Primary sclerosing cholangitis (PSC) is the most common known predisposing condition for this cancer. Cholangiocarcinoma rates of 8%–40% have been reported in patients with PSC in follow-up studies and in explanted specimens after liver transplantation.[31] Cholangiocarcinoma in these patients has a tendency to occur earlier, in the 30- to 50-year age-groups, than in sporadic cases.[28,32] Furthermore, about one-third of the PSC patients who develop cholangiocarcinoma do so within 2 years of diagnosis, and the risk of cholangiocarcinogenesis seems unrelated to the duration of the inflammatory disease.[32,33] Viral hepatitis has also been associated with cholangiocarcinoma.[34,35] Patients with cirrhosis induced by viral hepatitis revealed a significantly higher risk for this cancer compared to the general population.[35] Hepatitis B and C virus infection was frequently present in patients with cholangiocarcinoma.[36–38] Also, congenital abnormalities of the biliary tree associated with Caroli's syndrome, congenital hepatic fibrosis, and choledochal cysts carry a 15% risk of malignant change after the second decade, at an average age of 34 years.[39] The overall incidence of cholangiocarcinoma in patients with untreated biliary cysts varies up to 28%.[40,41] Hepatolithiasis, rare in the west, but relatively common in Asia, is also associated with cholangiocarcinoma.[31] Up to 10% of patients with hepatolithiasis develop cholangiocarcinoma.[42] Other causes and risk factors for cholangiocarcinoma are infestation with liver fluke, especially *Opisthorchis viverrini*,[43] and exposure to



		Primary recurrence
Liver	62 %	
Resection line	42 %	***76 %***
Regional lymph nodes	20 %	
Peritoneum	16 %	
Lungs	71 %	
Bones	31 %	***24 %***
Skin/Subcutis	7 %	

Fig. 2. Sites of recurrence after hilar resection for extrahepatic bile duct carcinoma in 22 patients[27]

chemical carcinogens, such as Thorotrast (thorium dioxide, ThO_2), a radiological contrast agent banned in the 1960s for its carcinogenetic properties, which has been strongly associated with the development of cholangiocarcinoma many years after exposure, increasing the risk to 300 times that in the general population.[31,44,45]

The challenge in dealing with many patients suffering from hilar cholangiocarcinoma in the context of an underlying liver disease, precluding a radical surgical approach with extended liver resection, has brought about new awareness of liver transplantation as a treatment option in the context of this cancer.

Current results

Recently reported results have shown increased survival rates after liver transplantation for hilar cholangiocarcinoma. The latest 1-, 3-, 5- and 10-year-survival rates of the 201 patients transplanted for hilar cholangiocarcinoma in Europe were 67%, 41%, 31%, and 22%, respectively (Fig. 3).[46] Iwatsuki et al.[47] reported a series of 27 patients with hilar cholangiocarcinoma who underwent liver transplantation, either because of the extent of the tumor or because of concomitant advanced cirrhosis, severe sclerosing cholangitis, or both, precluding partial hepatectomy. The 1-, 3- and 5-year survival rates in these patients were 59.3%, 36.2%, and 36.2%, respectively, with 7 patients surviving for more than 5 years. These long-term results included a perioperative mortality rate of 22.2%.[47] In a retrospective analysis from Meyer et al.,[48] including 207 patients with both hilar and intrahepatic cholangiocarcinomas over a period of almost 30 years, the 1-, 3- and 5-year survival rates were 60%, 42%, and 36%, respectively, including a postoperative 30-day mortality of 10%. Of the patients alive at the end of the study, the median follow-up after transplantation was 23 months, with 20 patients surviving for more than 3 years without recurrences. Eleven patients have survived for more than 5 years without recurrence.[48] The cumulative survival of 36 patients in a cohort from Spain was 55 ± 11 months; survivals at 1-, 3-, 5- and 10 years were 82%, 53%, 30%, and 18%, respectively.[49] In 5 patients with hilar cholangiocarcinoma treated by living-donor liver transplantation between December 1999 and May 2004 at our institution, none of the patients had tumor recurrence during follow-up that ranged from 7 to 36 months, whereas 1 of these patients died in the postoperative course after combined living-donor liver transplantation and pancreaticoduodenectomy.[50]

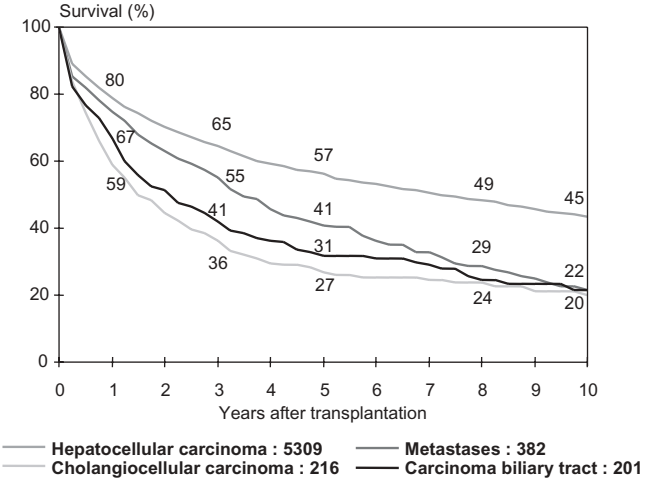


Fig. 3. Cumulative survival of 201 patients who received liver transplantation for hilar cholangiocarcinoma between May 1968 and December 2004 in European Liver Transplant Registry (ELTR) countries[46]

New adjuvant and neoadjuvant approaches

For further improvement of the results after liver transplantation for hilar cholangiocarcinoma, interest has been focused on adjuvant and neoadjuvant treatment options over the past few years. Clinical trials of new adjuvant and neoadjuvant protocols in highly selected patients have shown encouraging results. In a study by Sudan et al.[51] 11 patients with lymph node-negative hilar cholangiocarcinoma received liver transplantation after neoadjuvant radiochemotherapy. The protocol included brachytherapy delivered through percutaneous transhepatic catheters and intravenous infusion of 5-FU until transplantation. Five of the 11 patients (45%) were alive and free of tumor 2.8–14.5 years after transplantation.[51] A study from the Mayo Clinic treated 28 patients with unresectable, localized, and lymph node-negative stage I/II hilar cholangiocarcinoma with external-beam irradiation, systemic 5-FU, and brachytherapy with ^{192}iridium plus oral capecitabine before liver transplantation. Of the 28 patients, 3 died of perioperative complications and 4 developed recurrent cholangiocarcinoma 22–63 months after transplantation. The 1-, 3- and 5-year survival rates in this cohort were 92%, 82%, and 82%, respectively, a finding which is comparable to overall results for liver transplantation and better than survival rates after surgical resection.[52] However, in the evaluation of these encouraging results, it must be considered that these studies included only highly selected patients. Only patients with tumor stages I and II were selected for these studies. In addition, morbidity and mortality after neoadjuvant radiochemotherapy and liver transplantation were considerable. Vascular and septic complications were the most frequent causes of death during neoadjuvant treatment and after transplantation.[51,52] Therefore, further studies are necessary

to evaluate the safety and efficacy of neoadjuvant radiochemotherapy protocols.

Another new approach in the neoadjuvant treatment of hilar cholangiocarcinoma is photodynamic therapy (PDT). PDT has achieved remarkable regression of malignant tumors.[53–56] PDT is a two-step procedure: a photosensitizing drug known to accumulate in tumor cells is administered, after which the tumor is exposed to laser light of an appropriate wavelength. The activated photosensitizer forms cytotoxic reaction products, including singlet oxygen radicals that destroy cancer and neovascular cells and induce tumor thrombosis.[57–60] In some studies, PDT has been used in the palliative management of patients with hilar cholangiocarcinoma;[61,62] these authors reported that the median survival time of the patients was prolonged compared to that in other published reports and they noted that the patients' perception of their quality of life increased dramatically. In a single patient, neoadjuvant PDT for hilar cholangiocarcinoma showed complete destruction of the tumor, which was confined to the superficial 4 mm of the bile duct.[62] In a phase II study reported by Wiedmann et al.,[63] seven patients with advanced hilar cholangiocarcinoma were treated by PDT at the area of tumor infiltration and 2 cm beyond prior to surgical tumor resection. One of the seven patients received a combined liver transplantation and pancreaticoduodenectomy for an advanced Bismuth-Corlette type IV tumor with regional lymph node involvement, whereas the other patients were treated by combined hilar resection and partial hepatectomy. In a median follow-up after surgery of 16 months, two of these patients had died of recurrent disease, whereas the other patients were alive without evidence of tumor. The patient treated by liver transplantation and pancreaticoduodenectomy was alive and tumor-free 40 months after transplantation.[63] However, the experience with PDT in the context of hilar cholangiocarcinoma, in particular in combination with liver transplantation, is still sparse and further evaluation is needed to prove its value.

Further options for the improvement of survival rates after liver transplantation for hilar cholangiocarcinoma may come from new immunosuppressive agents, such as sirolimus (Rapamycin). Sirolimus was shown to have antiproliferative potency. In in vitro studies on hepatoma cell lines, sirolimus led to the suppression of cell proliferation, whereas calcineurin inhibitors promoted hepatoma growth.[64] In parallel, in an animal model, sirolimus inhibited, but cyclosporin promoted the growth of lung metastases in mice injected with murine colon cancer cells.[65] Furthermore, decreased tumor growth and tumor vascularization was seen in sirolimus-treated mice, but early neovascularization and accelerated tumor growth were seen with cyclosporin.[65] Sirolimus inhibited vascular endothelial growth factor secretion by tumor cell lines in vitro and in vivo.[65] In parallel to these experimental findings, Kneteman et al.[66] reported an excellent outcome in patients who were treated with a sirolimus-based immunosuppression regimen after liver transplantation for hepatocellular carcinoma; 21 of 40 patients in this series had extended tumor stages beyond the Milan criteria. The 1- and 4-year survival of the patients with extended tumor stages was 90.5% and 82.9%, respectively, which was not different compared to patients with tumors within the Milan criteria.[66] Four patients in the group with extended tumor stages and 1 patient with a tumor within the Milan criteria developed recurrence. Comparison of the fate of these patients with tumor recurrence on sirolimus therapy and the fate of patients in other series with hepatocellular cancer (HCC) recurrence on maintenance immunosuppression with calcineurin inhibitors showed a benefit for sirolimus-based immunosuppression.[66,67] Although, in the absence of a control group in this study,[66] conclusions about the prevention of tumor recurrence or prolonged survival after tumor recurrence could not be made, the results are encouraging. The experience with this new immunosuppressive agent is still small, in particular in the context of hilar cholangiocarcinoma, and therefore, further investigation is needed to explore its value in the management of patients receiving liver transplantation for this cancer. Nonetheless, new antiproliferative immunosuppressive agents may be useful to further improve the results after liver transplantation for hilar cholangiocarcinoma.

Current indications for liver transplantation in hilar cholangiocarcinoma

Currently, liver transplantation for the treatment of hilar cholangiocarcinoma should be taken into consideration in patients with underlying liver pathology that precludes liver resection. In particular, patients with PSC, who have a high incidence of this cancer, may be suitable for transplantation. Besides the existence of an underlying liver disease or cirrhosis, the tumor stage may be important for the indication. Recently published results have revealed a markedly improved outcome in patients with early tumor stages.[50,52] In particular, the absence of nodal involvement and a locally restricted character of the tumor seems to be correlated with favorable results after liver transplantation.[50,52] However, there are currently no generally accepted selection criteria for liver transplantation in patients with hilar cholangiocarcinoma; therefore, it may be recommended that liver transplantation as treatment for hilar cholangiocarcinoma should be performed only at centers with special interest in the treatment of this cancer.

Considerations regarding the selection of patients with malignant hepatic tumors for liver transplantation are largely influenced by the question of whether such use of cadaveric grafts would penalize other patients on the waiting list with nonmalignant liver diseases. This question does not arise in living-donor liver transplantation. In living-donor liver transplantation, a graft from a specific donor can exclusively be transplanted only to one specific recipient; therefore, the pool of cadaveric organs is not used and other patients are not put at a disadvantage. Furthermore, living donation eliminates the waiting time after listing, which prevents tumor progress until transplantation and offers the opportunity for an individual and time-wise planning of the treatment. However, living donation holds the risk of exposing a healthy donor to the risk of a major hepatectomy. Therefore, apart from the ethical aspects that have to be considered in living donation, the results in the liver-transplanted patients have to justify the risk for the donors. Therefore, careful patient selection is also needed in patients with hilar cholangiocarcinoma considered for living-donor liver transplantation.

Conclusions

Because of the relatively poor long-term survival rates, hilar cholangiocarcinoma does currently not represent a generally accepted indication for liver transplantation. However, careful patient selection and adjuvant treatment protocols have markedly improved the long-term results over the past decade. The establishment of generally accepted selection criteria and the combination with new adjuvant and neoadjuvant treatment protocols may help to further improve the long-term results, which may help to clarify the indications for liver transplantation as a treatment option in patients with hilar cholangiocarcinoma in the future.

References

1. Iwatsuki S, Gordon RD, Shaw BW, Starzl TE. Role of liver transplantation in cancer therapy. Ann Surg 1985;202:401–7.
2. Ringe B, Wittekind C, Bechstein WO, Bunzendahl H, Pichlmayr R. The role of liver transplantation in hepatobiliary malignancy. Ann Surg 1989;209:88–98.
3. Penn I. Hepatic transplantation for primary and metastatic cancers of the liver. Surgery 1991;110:726–34.
4. Pichelmayr R, Ringe B, Lauchart W, Bechstein WO, Gubernatis G, Wagner E. Radical resection and liver grafting as the two main components of surgical strategy in the treatment of proximal bile duct cancer. World J Surg 1988;12:88–98.
5. Bhuiya MR, Nimura Y, Kamiya J, Kondo S, Fukata S, Hayakawa N, Shionoya S. Clinicopathologic studies on perineural invasion of bile duct carcinoma. Ann Surg 1992;215:344–9.
6. Herbener T, Zajko AB, Koneru B, Bron KM, Campbell WL. Recurrent cholangiocarcinoma in the biliary tree after liver transplantation. Radiology 1988;169:641–2.
7. Kimura W, Nagai H, Atomi Y, Koruda A, Muto T, Yamashiro M, Esaki Y. Clinicopathological characteristics of hepatic hilar bile duct carcinoma. Hepatogastroenterology 1993;40:21–7.
8. Ouchi K, Suzuki M, Hashimoto L, Sato T. Histologic findings and prognostic factors in carcinoma of the upper bile duct. Am J Surg 1989;157:552–6.
9. Pichelmayr R, Weimann A, Steinhoff G, Ringe B. Surgical interventions of proximal bile duct tumors. Resectability, forms of resection and surgical palliative measures, liver transplantation — a critical evaluation of current status. Chirurg 1992;63: 539–47.
10. Bismuth H, Nakache R, Diamond T. Management strategies in resection for hilar cholangiocarcinoma. Ann Surg 1992;215:31–8.
11. Mimura H, Kim H, Ochiai Y, Takakura N, Hamazaki K, Tsuge H, et al. Radical block resection of hepatoduodenal ligament for carcinoma of the bile duct with double catheter bypass for portal circulation. Surg Gynecol Obstet 1988;167:527–9.
12. O'Grady JG, Polson RJ, Rolles K, Calne RY, Williams R. Liver transplantation for malignant disease. Results in 93 consecutive patients. Ann Surg 1988;207:373–9.
13. Arey LB. Developmental anatomy. 7th ed. Philadelphia: WB Saunders; 1974.
14. Starzl TE, Todo S, Tzakis A, Podesta L, Mieles L, Demetris A, et al. Abdominal organ cluster transplantation for the treatment of upper abdominal malignancies. Ann Surg 1989;210:374–86.
15. Alessiani M, Tzakis A, Todo S, Demetris AJ, Fung JJ, Starzl TE. Assessment of 5-year experience with abdominal organ cluster transplantation. J Am Coll Surg 1995;180:1–9.
16. Neuhaus P, Blumhardt G. Extended bile duct resectio — a new oncologic approach to the treatment of central bile duct carcinomas? Langenbecks Arch Chir 1994;379:123–8.
17. 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. Transpl Int 1998;11 (Suppl 1):206–8.
18. Neuhaus P, Jonas S, Bechstein WO, Lohmann R, Radke C, Kling N, et al. Extended resections for hilar cholangiocarcinoma. Ann Surg 1999;230:808–19.
19. Nimura Y, Kamiya J, Kondo S, Nagino M, Uesaka K, Oda K, et al. Aggressive preoperative management and extended surgery for hilar cholangiocarcinoma: Nagoya experience. J Hepatobiliary Pancreat Surg 2000;7:155–62.
20. Nagino M, Nimura Y, Kamiya J, Kanai M, Uesaka K, Hayakawa N, et al. Segmental liver resection for hilar cholangiocarcinoma. Hepatogastroenterology 1998;45:7–13.
21. Cameron JL, Pitt HA, Zinner MJ, Kaufman SL, Coleman J. Management of proximal cholangiocarcinomas by surgical resection and radiotherapy. Am J Surg 1990;159:91–7.
22. Meyers WC, Jones RS. Internal radiation for bile duct cancer. World J Surg 1988;12:99–104.
23. Hayes JK, Sapozink MD, Miller FJ. Definitive radiation therapy in bile duct carcinoma. Int J Radiation Oncol Biol Phys 1988;15:735–44.
24. Pitt HA, Nakeeb A, Abrams RA, Coleman J, Piantadosi S, Yeo CJ, et al. Perihilar cholangiocarcinoma. Postoperative radiotherapy does not improve survival. Ann Surg 1995;221:788–97.
25. Todoroki T. Chemotherapy for bile duct carcinoma in the light of adjuvant chemotherapy to surgery. Hepatogastroenterology 2000;47:639–43.
26. Takada T, Amano H, Yasuda H, Nimura Y, Matsushiro T, Kato H, et al.: Study Group of Surgical Adjuvant Therapy for Carcinomas of the Pancreas and Biliary Tract. 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: 1685–95.
27. Mittal B, Deutsch M, Iwatsuki S. Primary cancers of extrahepatic biliary passages. Int J Radiat Oncol Biol Phys 1985;11:849–54.

28. Pitt HA, Dooley WC, Yeo CJ, Cameron JL. Malignancies of the biliary tree. Curr Probl Surg 1995;32:1–90.
29. Makuuchi M, Thai BL, Takayasu K, Takayama T, Kosuge T, Gunven P, et al. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. Surgery 1990;107:521–7.
30. Vogl TJ, Balzer JO, Dette K, Hintze R, Pegios W, Maurer J, et al. Initially unresectable hilar cholangiocarcinoma: hepatic regeneration after transarterial embolization. Radiology 1998;208:217–22.
31. Shaib Y, El-Serag HB. The epidemiology of cholangiocarcinoma. Semin Liver Dis 2004;24:115–25.
32. Broome U, Olsson R, Loof L, Bodemar G, Hultcrantz R, Danielsson A, et al. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. Gut 1996;38: 610–5.
33. Bergquist A, Glaumann H, Persson B, Broome U. Risk factors and clinical presentation of hepatobiliary carcinoma in patients with primary sclerosing cholangitis: a case control study. Hepatology 1998;27:311–6.
34. Shaib YH, El-Serag HB, Davila JA, Morgan R, McGlynn KA. Risk factors for intrahepatic cholangiocarcinoma in the United States: a case control study. Gastroenterology 2005;128:620–6.
35. Sorensen HT, Friis S, Olsen JH, Thulstrup AM, Mellemkjaer L, Linet M, et al. Risk of liver and other types of cancer in patients with cirrhosis: a nationwide cohort study in Denmark. Hepatology 1998;28:921–5.
36. Shin HR, Lee CU, Park HJ, Seol SY, Chung JM, Choi HC, et al. Hepatitis B and C virus, *Clonorchis sinensis* for the risk of liver cancer: a case-control study in Pusan, Korea. Int J Epidemiol 1996;25:933–40.
37. Donato F, Gelatti U, Tagger A, Favret M, Ribero ML, Callea F, et al. Intrahepatic cholangiocarcinoma and hepatitis C and B virus infection, alcohol intake, and hepatolithiasis: a case control study in Italy. Cancer Causes Control 2001;12:959–64.
38. Kobayashi M, Ikeda K, Saitoh S, Suzuki F, Tsubota A, Suzuki Y, et al. Incidence of primary cholangiocellular carcinoma of the liver in Japanese patients with hepatitis C virus-related cirrhosis. Cancer 2000;88:2471–7.
39. Simeone DM. Gallbladder and biliary tree: anatomy and structural anomalies. In: Yamada T, editor. Textbook of gastroenterology. Philadelphia: Lippincott Williams & Wilkins.
40. Scott J, Shousha S, Thomas HC, Sherlock S. Bile duct carcinoma: a late complication of congenital hepatic fibrosis: case report and review of literature. Am J Gastroenterol 1980;73:113–9.
41. Lipsett PA, Pitt HA, Colombani PM, Boitnott JK, Cameron JL. Choledochal cyst disease: a changing pattern of presentation. Ann Surg 1994;220:644–52.
42. Kubo S, Kinoshita H, Hirohashi K, Hamba H. Hepatolithiasis associated with cholangiocarcinoma. World J Surg 1995;19: 637–41.
43. Watanapa P, Watanapa WB. Liver fluke-associated cholangiocarcinoma. Br J Surg 2002;89:962–70.
44. Khan SA, Carmichael PL, Taylor-Robinson SD, Habib N, Thomas HC. DNA adducts, detected by ^{12}P postlabelling, in human cholangiocarcinoma. Gut 2003;52:586–91.
45. Sahani D, Prasad SR, Tannabe KK, Hahn PF, Mueller PR, Saini S. Thorotrast-induced cholangiocarcinoma: case report. Abdom Imaging 2003;28:72–4.
46. European Liver Transplant Registry. Data analysis booklet 05/1968–12/2004. Paris: ELTR; 2004.
47. Iwatsuki S, Todo S, Marsh JW, Madariaga JR, Lee RG, Dvorchik I, et al. Treatment of hilar cholangiocarcinoma (Klatskin tumors) with hepatic resection or transplantation. J Am Coll Surg 1998;187:358–64.
48. Meyer C, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. Transplantation 2000;69: 1633–7.
49. Robles R, Figueras J, Turrion VS, Margarit C, Moya A, Vara E, et al. Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma. Ann Surg 2004;239:265–71.
50. Jonas S, Mittler J, Pascher A, Theruvath T, Thelen A, Klupp J, et al. Extended indication in living-donor liver transplantation: bile duct cancer. Transplantation 2005;80 (Suppl 1):101–4.
51. Sudan D, DeRoover A, Chinnakotla S, Fox I, Shaw B, McCashland T, et al. Radiochemotherapy and transplantation allow long-term survival for nonresectable hilar cholangiocarcinoma. Am J Transplant 2002;2:774–9.
52. Rea DJ, Heimbach JK, Rosen CB, Haddock MG, Alberts SR, Kremers WK, et al. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. Ann Surg 2005;242:451–8.
53. Hayata Y, Kato H, Konaka C, Amemiya R, Ono J, Ogawa I, et al. Photoradiation therapy with hematoporphyrin derivative in early and stage 1 lung cancer. Chest 1984;86:169–77.
54. Prout GR Jr, Lin CW, Benson R Jr, Nseyo UO, Daly JJ, Griffin PP, et al. Photodynamic therapy with hematoporphyrin derivative in the treatment of superficial transitional-cell carcinoma of the bladder. N Engl J Med 1987;317:1251–5.
55. Edell ES, Cortese DA. Photodynamic therapy in the management of early superficial squamous cell carcinoma as an alternative to surgical resection. Chest 1992;102:1319–22.
56. Sibille A, Lambert R, Souquet JC, Sabben G, Descos F. Long-term survival after photodynamic therapy for esophageal cancer. Gastroenterology 1995;108:337–44.
57. Nelson JS, Liaw LH, Orenstein A, Roberts WG, Berns MW. Mechanism of tumor destruction following photodynamic therapy with hematoporphyrin derivative, chlorin, and phthalocyanine. J Nat Cancer Inst 1988;80:1599–605.
58. Henderson BW, Dougherty TJ. How does photodynamic therapy work? Photochem Photobiol 1992;55:145–57.
59. Pass HI. Photodynamic therapy in oncology: mechanisms and clinical use. J Natl Cancer Inst 1993;85:443–56.
60. Wong Kee Song LM, Wang KK, Zinsmeister AR. Mono-L-aspartyl chlorin e6 (NPe6) and hematoporphyrin derivative (HpD) in photodynamic therapy administered to a human cholangiocarcinoma model. Cancer 1998;82:421–7.
61. Ortner MA, Liebetrith J, Schreiber S, Hanft M, Wruck U, Fusco V, et al. Photodynamic therapy of nonresectable cholangiocarcinoma. Gastroenterology 1998;114:536–42.
62. Berr F, Wiedmann M, Tannapfel A, Halm U, Kohlhaw KR, Schmidt F, et al. Photodynamic therapy for advanced bile duct cancer: evidence for improved palliation and extended survival. Hepatology 2000;31:291–8.
63. Wiedmann M, Caca K, Berr F, Schiefke I, Tannapfel A, Wittekind C, et al. Neoadjuvant photodynamic therapy as a new approach to treating hilar cholangiocarcinoma. Cancer 2003;97: 2783–90.
64. Schumacher G, Oidtmann M, Rosewicz S, Langrehr J, Jonas S, Mueller AR, et al. Sirolimus inhibits growth of human hepatoma cells in contrast to tacrolimus which promotes cell growth. Transplant Proc 2002;34:1392–3.
65. Guba M, von Breitenbuch P, Steinbauer M, Koehl G, Flegel S, Hornung M, et al. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. Nat Med 2002;8:128–35.
66. Kneteman NM, Oberholzer J, Al Saghier M, Meeberg GA, Blitz M, Ma MM, et al. Sirolimus-Based immunosuppression for liver transplantation in the presence of extended criteria for hepatocellular carcinoma. Liver Transpl 2004;10:1301–11.
67. Yao FY, Ferrell L, Bass NM, Bachetti P, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: comparison of the proposed UCSF criteria with the Milan criteria and the Pittsburgh modified TNM criteria. Liver Transpl 2002; 8:765–74.