

Hepatoma—resection or transplantation

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The most frequent tumors of the liver originate from the hepatocytes, bile duct epithelium, and endothelial cells. Hepatocellular carcinoma accounts for 80% to 90% of primary liver cancer. Cholangiocarcinoma, a neoplasm that arises from the biliary tree, is the second most common primary hepatic malignancy.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC), a primary malignant epithelial tumor that originates from hepatocytes, is the fifth most common cancer worldwide, being responsible for about 1 million deaths each year. The age-adjusted incidence rate of HCC varies widely between 20 to 28 cases per 100,000 in East Asia and in Middle Africa, and fewer than 5 per 100,000 in Northern Europe, North America, and Australia [1]. In the United States, a significant increase in the incidence from 1.4 to 2.4 cases per 100,000 has been observed during the last 2 decades [2]. Typically, the tumor develops within pathologically altered liver tissue. Because carcinoma itself and not the accompanying hepatic disorder accounts for disease-specific mortality, early tumor detection with an intent of curative treatment, either in terms of local resection or liver transplantation, presents the key issue in the management of the population at risk [3]. Without specific treatment the prognosis is poor, with a median survival of 1 to 2 months for patients with advanced tumors and 6 to 9 months for those with HCC in early stages [4].

Epidemiology and clinical presentation

Liver cirrhosis, either due to viral infection or high alcohol consumption, presents the main risk for HCC occurrence. Among cirrhotics, the 5-year

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cumulative incidence of HCC ranges between 7% and 20% [5,6]. Chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is the most powerful environmental etiologic prerequisite for the tumor. The mechanism of HCC development within the cirrhotic liver is still unclear; either the hepatitis virus itself acts directly as an oncogene or it contributes to hepatocarcinogenesis indirectly by the establishing of cirrhosis. Whereas in some Asian countries strong coincidence between HBV infection and HCC exists, in Europe and in the United States HCV viral genotype is more frequently found in patients suffering from HCC. Males who are positive for hepatitis B e antigen and hepatitis B surface antigen have significantly increased risk of developing HCC, as compared with those individuals who are negative for both antigens [7]. According to the experience in Taiwan, prophylactic vaccination against HBV may decrease the incidence of HCC in regions of high risk [8]. In Caucasian patients, most HCC, associated either with HBV or HCV infection, develops from hyperplastic lesions in cirrhotic livers. In the African or Asian populations, however, HCC may more often occur as de novo lesions within noncirrhotic liver tissue. Other predisposing factors are increasing age as an indicator for a long-standing cirrhosis, male gender, familial hemochromatosis, alpha 1-antitrypsin deficiency, chronic Budd-Chiari syndrome, primary biliary cirrhosis, mutations of the *p53* gene, and repeated exposure to oncogenic agents such as aflatoxin, particularly in the setting of pre-existing chronic hepatitis B, azo dyes, chlorinated hydrocarbons, or pesticides.

With a great geographic variability, the clinical presentation of patients with HCC depends on the tumor stage. It varies widely from an asymptomatic condition, in the case of an incidentally discovered small lesion, to general deterioration, upper abdominal pain, weight loss, jaundice, hepatic dysfunction, and palpable abdominal mass. Considering an estimated tumor doubling time of 4 to 6 months, in untreated patients a median survival of less than 12 months can be expected [4]. The identification of the at-risk population and the recognition of the significant morbidity and mortality associated with advanced HCC led to the development of surveillance strategies, with the aim to either prevent tumor development by prophylactic antiviral therapy or to detect the carcinoma at an early stage, when a potentially curative treatment can be offered [9]. With regard to cost-effectiveness, patients with Child-Pugh's class A cirrhosis that are suitable candidates for resection or Child-Pugh's class C patients considered for liver transplantation should be included in screening programs.

Diagnostic confirmation and classification

For the patients at risk of developing HCC, the majority of surveillance protocols include percutaneous ultrasound (US), with a reported sensitivity and specificity of 71% and 93%, respectively, and alpha-fetoprotein (AFP) measurement, with a reported sensitivity of 40% to 64% and specificity of

75% to 91%, as the basic tools that should be repeated every 6 months [10]. In an Italian study, screening based on this recommendation disclosed HCC in 5.9% of 1125 hepatitis-positive patients [11]; however, the tumor was still resectable in fewer than 50% of these patients. Upon sonographic disclosure of a suspicious lesion less than 1 cm in diameter, US should be repeated every 3 months to detect tumor growth as an indicator for malignancy. In the presence of a nodular mass > 1 cm or pathologic AFP values, further imaging studies should be undertaken. Helical computed tomography (CT) with arterial and portal phase images, and dynamic multiphase gadolinium-enhanced magnetic resonance imaging (MRI) showing tumor enhancement during the arterial phase are the most appropriate complementary techniques [12,13]. In cirrhotic patients considered for liver transplantation, contrast-enhanced MRI should be performed every 6 months to detect HCC at an early stage, with an option of local tumor treatment as bridging during the waiting time for a suitable graft [14]. The diagnostic value of percutaneous fine-needle biopsy is controversial. Although a negative result does not exclude malignancy and 2% to 3% incidence of needle-tract seeding has to be taken into account [15], molecular characterization of a tumor specimen obtained by a biopsy could be an important criterion for better selection of treatment modalities. Despite the use of advanced imaging methods, the differentiation between HCC and dysplastic nodules remains difficult. In 20% to 60% of cases, multifocal tumor growth in terms of synchronous or metachronous hepatocarcinogenesis is observed [16]. It has to be stressed that, independently of the imaging method used, a significant portion of HCCs are underscored in their stage when compared with intraoperative findings or pathologic analysis of explanted livers [14,17].

The stage, aggressiveness, and growth pattern of the tumor, the severity of the underlying cirrhosis, the general condition of the patient, and the effectiveness of the treatment modality applied are factors delimiting the prognosis of HCC patients. To identify prognostic predictors and discriminate different treatment strategies, several clinical scoring systems have been developed. The TNM (tumor, node, metastasis) staging, Karnofsky index, or Child-Pugh classification are of limited relevance, because they consider only a singular variable. The Okuda classification encompasses bilirubin, albumin, ascites, and tumor mass. Although widely used, the prognostic predictability of this system is questionable because it cannot distinguish between different tumor stages [4]. The Barcelona-Clinic liver cancer staging classification takes into consideration four stages, based on clinical parameter and treatment modalities [18]. For patients at an early stage (asymptomatic solitary HCC <5 cm in size or up to 3 nodules <3 cm) with access to potentially curative treatment options (ie, resection, liver transplantation, percutaneous ablation), a 5-year survival rate can be expected. In contrast, for symptomatic patients with aggressive tumors and no efficient treatment possibilities, a 3-year survival rate of only 10% has to be calculated. New multidimensional systems such as the Cancer of the

Liver Italian Program (CLIP) score [19] or the classification developed by Chevret et al [20] need further evaluation to verify their discriminatory ability and clinical value.

Treatment

Several therapeutic approaches have been developed as invasive or noninvasive strategies for HCC treatment. So far, there is no generally accepted therapeutic algorithm that can be applied worldwide in different cohorts of patients. Because randomized controlled clinical studies are not available, unequivocal recommendation on the first-line treatment cannot be given. Consequently, centers develop their own strategies, based on the results of single-cohort studies and their own experience and resources. Surgical resection and liver transplantation have been advocated as the only therapies with potentially curative intent.

Liver resection

Over the past recent years, clinical implementation of early detection strategies for HCC has significantly increased the number of patients undergoing liver resection. Oncologically adequate hepatic resection is the treatment of choice for noncirrhotic patients with tumors <5 cm in size. Additionally, patients with Child-Pugh class A liver cirrhosis with normal or only moderately elevated bilirubin values (<1.9 mg/dl) in the absence of portal hypertension are considered as candidates for parenchyma-sparing liver resection, either in terms of left hepatectomy, sectoriectomy of the right hemiliver, central hepatectomy, or segmentectomy and subsegmentectomy only [21–25]. During the operation, ultrasonography should be performed to disclose multifocal tumor growth and identify the optimal direction of parenchymal transection. Even in high-volume centers, the resection rate is low, varying between 16% in the United States [26] and 33% in the Asian experience [25]. In the presence of Child-Pugh class B or C cirrhosis with single HCC less than 5 cm or three nodules smaller than 3 cm, liver transplantation is considered as the first-line therapy by the majority of centers.

Advances in perioperative management, in combination with new surgical techniques and better patient selection, have significantly lowered the operative morbidity and mortality after resection of HCC as compared with historical experience [27]. In institutions with extensive experience in hepatobiliary surgery, 3-year and 5-year survival rates from 68% to 76% and 51% to 68%, respectively, and a mortality rate of less than 2% have been reported [18,24,28–31]. A long-term study from Japan on hepatic resection in 303 patients with HCC revealed a 30-day mortality of 1.6%, a 3-year survival rate of 67%, and a 10-year survival rate of 20%. Among long-term survivors, 27% and 11% were tumor-free after 5 and 10 years, respectively (Table 1) [32]. For resected patients in general, a 5-year survival rate of 50% is considered as the minimal cutoff value. The impairment of

Table 1
Liver resection and liver transplantation for hepatocellular carcinoma

	Year	Number of patients	Actuarial survival rate	
			3 year	5 year
Liver resection			%	%
Fuster et al [30]	1996	48	64	–
Fong et al [29]	1999	38	63	57
Llovet et al [23]	1999	77	62	51
Wayne et al [24]	2002	45	76	68
Arii et al [28]	2002	2722	–	58
Kanematsu et al [32]	2002	303	67	51
Yamamoto et al [31]	2001	58	–	61
Own experience ^a	2003	139	65	–
Liver transplantation				
Penn et al [50]	1991	365	–	18
Iwatsuki et al [55]	2000	220	46	37
Collela et al [77] ^b	1997	71	81	61
Figueras et al [56]	2001	85	76	60
Tamura et al [78]	2001	53	81	78
Jonas et al [57]	2001	120	–	71
Hemming et al [58]	2001	112	63	57
Own experience ^{a,c}	2003	46	61	–

^a Department of General Surgery and Transplantation, University Hospital Essen, Germany, time period: 01/04/1998–30/04/2003.

^b With adjuvant systemic or local chemotherapy.

^c Patients with incidentally discovered HCC and patients with HCC known prior to liver transplantation. The fibrolamellar HCC subtype is included.

liver function significantly triggers the postresectional outcome, as even Child-Pugh class A patients are at high risk of developing refractory ascites [30]. Factors that may help determine the risk of operative mortality are the degree of portal hypertension and serum bilirubin levels [5]. In the experience from Taiwan, centrally located tumors, serum albumin levels, and indocyanine green retention rate are parameters influencing outcomes after resection of HCC <3 cm [33]. Due to the International Cooperative Study Group on Hepatocellular Carcinoma, a scoring system encompassing liver fibrosis score, Edmondson-Steiner grade, and Child-Pugh class enables the selection of patients with HCC <5 cm for resection [24]. Recently developed imaging techniques, such as CT in three-dimensional technique, may contribute to better preoperative estimation of patient-specific liver anatomy and the volume of residual liver tissue. In selected patients with insufficient functional hepatic reserve, embolization of the right portal vein can contribute to safe secondary tumor resectability [34].

The data concerning the outcome of patients with HCC larger than 5 cm in size are controversial. Although in some reports the outcome was dismal [35], others present results as favorable as in case of tumors less than 5 cm [36]. Only a few studies deal with perioperative and long-term outcome after

hepatic resection for HCC larger than 10 cm in diameter. In the experience of Japanese groups, operative mortality in this particularly demanding cohort of patients was as high as 14.3%, and 3-year and 5-year survival rates were only 25% and 8.2%, respectively [37,38]. Astonishing results were obtained in a recent study, from a group in Hong Kong that achieved a 5-year survival rate of 38.2% in a selected collective of noncirrhotic patients with solitary HCC > 10 cm in the absence of macroscopic venous invasion [39]. The same group advocates that resection is feasible even in the subgroup of patients with TNM Stage IVA (T4, any N, M0, according to the International Union Against Cancer [UICC] classification from 1997) HCC without evidence of portal or hepatic vein involvement, because these patients are not eligible for any alternative treatment [40].

Unfortunately, long-term surgical results for HCC are burdened with 3-year and 5-year tumor recurrence rates of 50% and 75% to 100%, respectively [28,35,41,42]. The manifestation of HCC recurrence is manifold; the tumor can present in the form of intrahepatic metastases, as a slowly growing, unrecognized at the time of primary surgery, synchronous, multicentric carcinoma; or as a metachronous multilocal malignancy. Whereas intrahepatic metastases are frequently seen in advanced primary tumors with vascular invasion, metachronous multilocal tumor growth more often corresponds with smaller HCC. In addition to pathologic tumor characteristics, the severity of the accompanying liver disease again plays a crucial role, because the condition itself acts as a preneoplastic state. At significant risk are patients with a positive HCV status and markedly elevated preoperative serum aspartate aminotransferase levels [43,44]. The preventative effect of polyprenic acid, intra-arterial I¹³¹-labeled lipiodol, alpha-interferon, diethyl nitrosamine, or adoptive immunotherapy is the subject of current studies [5]. In selected patients with extra- or/and intrahepatic recurrence, an aggressive surgical approach may be justified (median survival 44.0 months in the resected group versus 10.6 months in the nonsurgically treated group) [42,45].

Liver transplantation

Theoretically, orthotopic liver transplantation (OLT) presents the best treatment for HCC, because it provides normal liver function after radical elimination of a potentially multicentric malignancy and associated end-stage liver disease. During the pioneer period of OLT, this new treatment option was rather liberally offered to cancer patients, regardless of their tumor stage. Initial results were disappointing; more than 60% of cases developed tumor recurrence within the first two post-transplant years [46,47]. Early studies reported 1-year and 5-year survival rates of 42% to 71% and 20% to 45%, respectively [48,49]. The Cincinnati Transplant Tumor Registry described a 5-year survival rate as low as 18% [50]. Of the few patients who survived, only 9% were free of tumor 2 years postoperatively. Better results have been obtained, however, when HCC was

discovered incidentally or in the presence of fibrolamellar tumor subtype, listed in **Box 1**. This suggested that liver transplantation may be a reasonable treatment for patients with early-stage tumors in cases where resectability cannot be achieved. The uniformly dismal experiences have prompted several centers to either radically omit patients with known HCC from a waiting list for transplantation, or to accept only those with smaller tumors. Subsequent series proved that better results are achievable by applying stringent selection criteria, such as TNM classification, and that selected HCC patients are likely to have long-term outcomes comparable to those of transplanted cirrhotics without malignancy [51]. At present, the majority of transplantation programs consider cirrhotic patients with small HCC (UICC Stage I or II) as suitable candidates [52,53]. In contrast, for UICC Stage IV tumors, the indication for transplantation is questionable, due to the dismal 5-year survival rates of 19% to 20% achieved by the majority of centers (see **Table 1**).

In consideration of limited organ availability and theoretically elevated cancer recurrence rate under immunosuppression, efforts have been made to identify patients who would benefit from OLT. The Milan score, as developed by Mazzaferro et al in 1996, has been used as a basic stratification

Box 1. Modified TNM staging classification for HCC [54]

T0 tumor not found

T1 one nodule, 1.9 cm

T2 one nodule, 2.0–5.0 cm; two or three nodules, all 3.0 cm

T3 one nodule, >5.0 cm; two or three nodules, at least one >3.0 cm

T4a T2, T3, or T4a plus gross intrahepatic portal or hepatic vein involvement as indicated by CT, MRI, or ultrasound

N1 regional (porta hepatis) nodes, involved

M1 metastatic disease, including extrahepatic portal or hepatic vein involvement

Stage I T1

Stage II T2

Stage III T3

Stage IVA1 T4a

Stage IVA2 T4b

Stage IVB any N1, any M1

Modified from: American Liver Tumor Study Group. TNM staging classification for HCC. A randomized prospective multi-institutional trial of orthotopic liver transplantation or partial hepatic resection with or without adjuvant chemotherapy for hepatocellular carcinoma. Investigator Booklet and Protocol. Chicago, IL: American Joint Committee on Cancer; 1998.

tool by numerous transplantation centers worldwide and integrated into the generally used American Liver Tumor Study Group Modified TNM Staging Classification for HCC (see **Box 1**) [51,54]. Presence of a single tumor 5 cm or less in size and no more than three nodules (each 3 cm or less in size in cases of multilobar tumor spread) were considered as criteria for transplantation. In the group of patients who met these criteria, 4-year overall and tumor-free survival were 85% and 92%, respectively, whereas the corresponding rates dropped to 50% and 59% in the patients with larger tumor bulk. Additional variables such as TNM status, the number of tumors, the serum AFP level, the Child-Pugh class, age, and sex had no significant prognostic input.

When analyzing several tumor-related and clinical or demographic parameters, it was shown that survival after OLT is affected by pT4 tumor stage and total tumor diameter only (University of California, San Francisco [UCSF] criteria) [54]. Iwatsuki et al identified bilobar tumor distribution, size of the greatest tumor (2 to 5 cm and > 5 cm), and vascular invasion (microscopic versus macroscopic) as strong risk factors for tumor recurrence, and calculated five groups of risk scores [55]. They suggested that only patients with grade 1 or 2 should undergo liver transplantation (5-year survival 100% and 61%, respectively), whereas patients with grades 4 or 5 should be excluded from this procedure (5-year survival 5% and 0%, respectively). In a retrospective multicentric study from Spain, macroscopic vascular invasion and AFP levels exceeding 300 ng/ml were associated with dismal prognosis [56]. Vascular invasion and histopathologic grading were found to be the strongest predictors of disease recurrence in other studies [57,58]. Due to the initial data collected by the International Registry of Hepatic Tumors in Liver Transplantation, transplanted patients with incidentally discovered HCC had the same prognosis as those in whom the malignant diagnosis was already known before surgery. The long-term outcome after transplantation for the fibrolamellar HCC subtype was comparable to that for the common HCC type. Concerning early post-transplant survival, the data were in favor of the fibrolamellar HCC cohort [53]. The recent update of the Registry based on analysis of 790 transplanted HCC patients, 3% of these with the fibrolamellar subtype, disclosed histologic grade, tumor size > 5 cm, and lymph node metastases to be significant factors that influence survival [59]. Tumor-free survival was determined by tumor size > 5 cm, positive lymph-node involvement, bilobar spread, and vascular invasion [53,59].

To improve disease-free survival following liver transplantation for HCC, perioperative adjuvant chemotherapy and bridging interventions such as chemoembolization, radiofrequency ablation, or percutaneous ethanol injection therapy are recommended by some institutions for patients while on the waiting list. For HCCs larger than 5 cm in size, encouraging overall and disease-free long-term survival was achievable by a subselective arterial chemoembolization with mitomycin C, doxorubicin, and cisplatin before

transplantation, followed by intraoperative and postoperative systemic doxorubicin administration [60]. Again, large tumors and vascular invasion presented predictors for poor outcome. When considering cost effectiveness, adjuvant therapy is recommended only for those patients who wait more than 1 year. For shorter waiting periods, percutaneous tumor ablation achieves a marked benefit. Because in most of the transplanted HCC patients the malignancy develops in the presence of underlying hepatitis B or C related cirrhosis, a post-transplant reinfection can lead to a late graft failure. By prophylactic use of hepatitis B immunoglobulin, lamivudine, or a combination of both, improved survival rates are achievable in this high-risk cohort of patients [58]. In addition, HCV reinfection has been reported to harbor a 40% risk of de novo HCC occurrence in a transplanted graft [61].

One of the key issues of liver transplantation for HCC is the long waiting time for transplantation, due to worldwide shortage of cadaveric grafts. While waiting, patients are at risk of tumor progress or disease deterioration, and consequent dropout from the waiting list. In a recently published analysis, cumulative likelihood for dropout at 6, 12, and 24 months for patients put on the waiting list from 1998 to 2001 amounted to 7.3%, 25.3%, and 43.6%, respectively. Risk factors for dropout were two or three nodules, solitary tumor > 3 cm in size at initial diagnosis, and previous liver resection [62]. According to the United Network for Organ Sharing (UNOS), HCC patients in Stage I/II have to be registered as status 2B; a condition that was associated in the United States in 1999 with a waiting time of 11 to 150 days [63]. For those patients classified as status 3 (HCC in Stage III), the waiting time was even longer. The impact of the newly introduced Model for End-Stage Liver Disease (MELD) schema (which ranks cirrhotic patients according to their risk for death) on the allocation problems in patients with HCC needs to be defined. Living-donor liver transplantation (LDLT) offers an attractive option to avoid the problems of the waiting list associated with cadaveric donation. A group from Barcelona calculated recently that, in terms of cost-effectiveness and under consideration of the exclusion rate (4% monthly), the complication rate of donors (0.5% to 1% mortality), and the procedure-specific costs, the LDLT is superior to cadaveric liver transplantation when waiting times are longer than 7 months [63]. In addition, it allows expanding the present criteria and including patients in advanced tumor stages in transplantation programs.

Review of hepatocellular carcinoma

Only a small portion of the HCC patients presented at referral centers may receive surgical treatments in curative intent, as poor underlying liver function and tumor number often preclude standard hepatic resection. Liver resection is the first-line therapy in patients with HCCs smaller than 5 cm in diameter in the presence of well-preserved liver function. In surgically resected series, the 3-year and 5-year survival rates have been reported to be

68% to 76% and 51% to 68%, respectively. Duration of response to treatment is a critical issue, however, because tumor recurrence—either in terms of intrahepatic metastases, or metachronous HCC deposits in cases of multifocal tumor growth—occurs in a significant portion of resected patients. Among those who enjoy long-term survival, less than 30% are tumor-free after 5 years. Increased risk for local tumor recurrence is predicted by histomorphological factors such as vascular invasion and poor differentiation degree. In addition, underlying liver cirrhosis itself acts as precancerosis.

Total hepatectomy with consecutive liver transplantation has the advantage of en bloc elimination of the affected liver and the malignant disease. Initial results of OLT for HCC were burdened with local tumor recurrence in up to 80% of patients. Through consequent use of strict selection criteria (ie, tumor size and number, vascular invasion, and histopathologic grading) better results were achievable. In patients who correspond to these criteria, a 5-year survival rate of approximately 60% is reported. The lack of available organs and prolonged waiting times for transplantation associated with possible tumor progression are the key issues of OLT. In consideration of a waiting time of 12 months, the likelihood of tumor progress and dropout from the waiting list is approximately 25%. Living-donor liver transplantation may overcome these problems in the future.

Intrahepatic cholangiocarcinoma

Cholangiocarcinoma (CCC) is an epithelial tumor that originates from the biliary system and presents with an incidence of 1 or 2 per 100,000 in the United States. It accounts for approximately 5% of the primary liver tumors. Intrahepatic (peripheral) cholangiocarcinoma (ICC) should be distinguished from extrahepatic (central) CCC and gallbladder cancers, because the tumors show different histological structures and clinical behaviors. Most ICCs are adenocarcinoma, papillary carcinoma, or mucinous carcinoma. Although the mortality from ICC is increasing worldwide, decreased mortality from extrahepatic tumors, particularly in the female population, has been observed [64].

Epidemiology and clinical appearance

The frequency of ICC is higher in Asian countries than in the Western world. In contrast to HCCs, most ICCs develop within normal liver tissue. Chronic biliary-tree inflammation has been documented as a major risk factor for the development of ICC. In the United States and some other Western countries, primary sclerosing cholangitis (PSC) and ulcerative colitis are risk factors documented in several patients suffering from ICC. In all newly diagnosed patients with PSC screening for ICC based on endoscopic biliary brush cytology or biopsies, measurement of serum CA

19-9 and positron emission tomography (PET) scanning is recommended. In the Far East, hepatolithiasis and parasitic infections are additional factors supporting carcinogenesis of ICC. At diagnosis, patients present with abdominal pain, fatigue, weight loss, and gradually progressive jaundice.

Diagnostic confirmation and staging

Laboratory analysis reveals increases of serum alkaline phosphatase, bilirubin, and gamma glutamyltransferase. In the majority of cases, ultrasonography and CT, as the initial diagnostic imaging procedures, detect intrahepatic mass. For preoperative staging purposes, MRI permits accessing precious information concerning intrahepatic tumor extension, and assessment of biliary tree and vascular structures. Additionally, MRI may detect regional lymph-node involvement and distant intra-abdominal metastases. In contrast to HCC, PET is a sensitive diagnostic tool for identification of ICC already in early tumor stages. Intrahepatic cholangiocarcinomas are staged according to TNM classification (Table 2) [65].

Treatment

Liver resection

For patients subjected to hepatic resection, complete tumor removal with a free margin is the only treatment option that may provide improved survival [66]; however, long-term survival will be achieved in only 20% of cases [67]. Standard operative procedure is hepatectomy combined with extensive lymph-node dissection. Factors influencing survival are tumor-free margin, lymph node metastases, and histopathology of the tumor. After curative resection, median survival ranges from 8 to 59 months [68–70]. In a recent study from Japan, a 5-year survival rate of 43% has been documented for patients with peripheral-type tumors, whereas in the group of patients with tumors invading hepatic hilus, the 5-year survival rate did not exceed 4% [71]. In addition, the incidence of perineural invasion and lymph-node involvement was associated significantly with hilar-invasive type tumors. Over 58% of the patients had lymph node metastases and no patient with lymph node involvement survived more than 38 months. Nodal involvement was also related to perineural invasion, invasion of the hilar bile duct or portal vein, and microscopically positive margins.

Liver transplantation

Liver transplantation theoretically offers the only treatment option for the significant portion of patients with ICC who present with unresectable tumor load. Due to the rarity of the tumor, single-center experiences on survival of ICC patients after OLT are limited. The Cincinnati Transplant Tumor Registry reviewed the data of 207 patients worldwide who underwent OLT for unresectable cholangiocarcinoma [72]. The 1-, 2-, and

Table 2
Staging for ICC according to TNM classification [65]

Stage	T (tumor)	N (nodes)	M (metastases)
I	T1	N0	M0
II	T2	N0	M0
III	T1,	N1	M0
	T2	N1	M0
	T3	N0	M0
	T3	N1	M0
IV A	T4	Any N	M0
IV B	Any T	Any N	M1

Abbreviations: T1, solitary tumor <2 cm, without vascular invasion; T2, solitary tumor <2 cm, with vascular invasion, or multiple tumors in one lobe, all <2 cm, without vascular invasion, or solitary tumor >2 cm without vascular invasion; T3, solitary tumor >2 cm with vascular invasion, or multiple tumors in one lobe, all <2 cm, with vascular invasion, or multiple tumors >2 cm in one lobe with and without vascular invasion; T4, multiple tumors in more than one lobe or invasion of major portal or hepatic venous branch.

M0, no distant metastasis; M1, distant metastasis; N0, no lymph node involvement; N1, lymph node metastasis.

From American Joint Committee on Cancer. Staging for ICC according to TNM classification. Liver (including intrahepatic bile ducts). In: Beahrs OH, Henson DE, Hutler RVP, editors. Manual for staging of cancer, 4th Edition. Philadelphia. Lippincott, 1992, p. 89–90.

5-year survival rates were 72%, 48%, and 23%, respectively. These data confirmed experiences gained in single-center series [69,73]. In 51% of the patients, tumor recurrence occurred after OLT, and 84% of recurrences were diagnosed within the first 24 months after transplantation. As seen in the cohort of resected patients, hilar-node involvement was associated with dismal prognosis. Survival in the group of patients with incidentally discovered ICC was not significantly better than in the group with clinically evident tumors. No prognostic variables were identifiable. In smaller published series, 3-year disease-free survival rates ranged from 13% to 53%, with recurrence rates between 27% and 87%. Allograft was the most common site of recurrence, followed by the lungs. This observation suggests that residual tumor cells in the perihepatic lymphatics of the recipient and distant micrometastasis were present at the time of OLT.

Recently, Shimoda et al reported on a 3-year disease-free survival rate of 30% in a group of 16 patients transplanted for ICC [74]. Small tumor size, single tumor foci, and the absence of contiguous organ invasion were prognostic factors associated with better outcome. The authors concluded that only selected patients with small ICCs should be offered OLT. Particularly in patients with PSC, efforts should be made to diagnose ICC at an early stage, because encouraging results have been reported in single series for this high-risk population [73,75].

The impact of adjuvant therapy on the prognosis of patients transplanted for ICC remains unclear. For highly selected patients with early-stage ICC, a group from the Mayo Clinic developed an aggressive adjuvant treatment

protocol including external-beam irradiation and bolus 5-fluorouracil (5-FU), followed by brachytherapy and protracted venous infusion with 5-FU, and subsequent OLT [76].

Review of intrahepatic cholangiocarcinoma

Intrahepatic CCC frequently presents in advanced unresectable stages. In a small number of patients eligible for surgical therapy, aggressive resection with tumor-free margins and extended lymphadenectomy may provide long-term survival in 20% of cases. Due to the high rate of local tumor recurrence and the lack of reliable prognostic variables, liver-transplantation OLT is seldom indicated in the presence of ICC. The 2- and 5-year survival rates do not exceed 48% and 23%, respectively. Using stringent selection criteria, the 3-year disease-free survival amounts to 30%. Identification of prognostic factors and development of more effective adjuvant therapies are desirable to improve the prognosis of patients with ICC and to enlarge the indications for OLT.

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