ESMO Open Cancer Horizons

Cancer and liver cirrhosis: implications on prognosis and management

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To cite: Pinter M, Trauner M, Peck-Radosavljevic M, *et al*. Cancer and liver cirrhosis: implications on prognosis and management. *ESMO Open* 2016;**1**:e000042. doi:10.1136/esmoopen-2016-000042

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/esmoopen-2016-000042).

MP, MP-R, and WS Liver Cancer (HCC)-Study Group Vienna.

Received 4 February 2016
Accepted 6 February 2016

Find educational slides on the treatment of liver metastases here: http://oncologypro.esmo.org/content/download/14408/256340/file/optimal-treatment-liver-metastases-2012.pdf.

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ABSTRACT

Liver cirrhosis, the end-stage of every chronic liver disease, is not only the major risk factor for the development of hepatocellular carcinoma but also a limiting factor for anticancer therapy of liver and non-hepatic malignancies. Liver cirrhosis may limit surgical and interventional approaches to cancer treatment, influence pharmacokinetics of anticancer drugs, increase side effects of chemotherapy, render patients susceptible for hepatotoxicity, and ultimately result in a competitive risk for morbidity and mortality. In this review, we provide a concise overview about the impact of liver cirrhosis on the management and prognosis of patients with primary liver cancer or non-hepatic malignancies.

INTRODUCTION

A significant number of patients with cancer concomitantly suffer from liver cirrhosis for several reasons. First, the fact that both diseases are relatively common among the general population increases the probability of suffering from both diseases simultaneously. Cancer is a leading cause of death and its incidence is expected to rise globally due to the growth and aging of the population. It has been estimated that there were more than three million new cancer cases in Europe and 14.1 million new cases globally in 2012.[1] Despite significant progress in the knowledge and management of liver disease over the past decades, liver cirrhosis still represents a major health burden.[2] About 0.1% of the European population suffers from cirrhosis even though the intra-European variation is large. The annual incidence rate is around 14–26 per 100,000 inhabitants and approximately 170,000 people die from complications of cirrhosis per year.[3] Second, liver cirrhosis is a well-known risk factor for primary liver cancer[4 5] but also increases the risk of developing extrahepatic malignancies.[6] Finally, both diseases have certain risk factors in common including smoking, alcohol abuse, and metabolic syndrome.[7–12] The issue of comorbidity implicates a major challenge in daily clinical practice. Optimal patient management requires comprehensive knowledge of both diseases and an interdisciplinary approach involving surgeons, interventional radiologists, oncologists and hepatologists.

In this review we discuss the staging and outcome of patients with liver cirrhosis and the influence of the severity of underlying liver cirrhosis on prognosis and management of patients with primary liver cancer and non-hepatic cancer.

LIVER CIRRHOSIS

General

Liver cirrhosis represents the final stage of liver fibrosis, the wound healing response to chronic liver injury. Cirrhosis is characterised by distortion of the liver parenchyma associated with fibrous septae and nodule formation as well as alterations in blood flow.[13] The natural course of fibrosis begins with a long-lasting rather asymptomatic period, called 'compensated' phase followed by a rapidly progressive phase, named 'decompensated' cirrhosis characterised by clinical signs of complications of portal hypertension and/or liver function impairment (ie, ascites, variceal bleeding, encephalopathy, jaundice).[14–16] Patients with decompensated cirrhosis live significantly shorter than those with compensated disease (median survival, around 2 vs >12 years).[14 17] The development of other complications including refractory ascites, hepatorenal syndrome, hepatopulmonary syndrome or spontaneous bacterial peritonitis can further worsen the course of disease.[14] Hepatocellular carcinoma (HCC), the most common primary liver cancer, can develop at any stage of cirrhosis.[4 14] Liver transplantation often represents the only possibility of cure for liver cirrhosis and can improve survival and quality of life in selected patients with end-stage liver disease.[14 18]

Staging of liver cirrhosis

Prognostic models and staging systems are inevitable for adequate management of patients with liver cirrhosis, especially when it comes to selecting patients for liver transplantation.[19] Several classifications and prognostic models have been proposed in recent years of which the three most widely used staging systems are subsequently described briefly.

The Child-Pugh score was initially developed about 50 years ago to predict the prognosis after surgery for portal hypertension (portocaval shunting, transection of oesophagus) in patients with liver cirrhosis.[20] The original score was slightly modified later on and since then includes the following five variables: grade of encephalopathy and ascites as well as serum bilirubin, albumin and prothrombin time (table 1).[21] Sometimes prothrombin index or international normalised ratio (INR) are used instead of prothrombin time.[19] One to three points can be assigned for each variable and according to the sum of these points patients can be divided into three prognostic subgroups: Child-Pugh classes A (5–6 points), B (7–9 points), and C (10–15 points).[19 21] The 1-year survival rate for the stages A, B and C is approximately 95%, 80% and 44%, respectively (table 1).[14]

The main limitations of the Child-Pugh score are the empirical cut-off values of laboratory parameters and the inclusion of clinical variables needing subjective assessment (ie, encephalopathy and ascites).[19]

The Model for End-Stage Liver Disease (MELD) score was originally designed to assess the outcome after transjugular portosystemic intrahepatic shunt implantation in patients with liver cirrhosis.[22] A slightly modified version was proposed shortly thereafter aiming to assess the early (3 months) mortality risk for patients on the liver transplantation waiting list.[23] A simplified version (exclusion of variable 'cause of cirrhosis') was finally proposed and its ability to estimate 3-month mortality in liver transplant candidates with chronic liver disease was prospectively evaluated.[24] Using the three variables serum bilirubin, creatinine and INR the score can be calculated by means of the formula: $9.57\times\log_e$ (creatinine mg/dL)$+3.78\times\log_e$ (bilirubin mg/dL)$+11.20\times\log_e$ (INR) $+6.43$.[24] Bilirubin, creatinine and INR levels below 1 are rounded off to 1 in order to avoid negative logarithmic values, creatinine is limited to a maximum of 4 mg/dL to limit the ranking advantage granted to patients with end-stage renal disease, and the score was empirically capped at 40 for liver transplantation listing purposes. Consequently, the MELD score can achieve values between 6 and 40.[19 24] The MELD model was implemented for liver allocation to patients listed for liver transplantation in the Unites States and with modifications in several European countries in 2002 and 2006, respectively.[25 26] Among patients with MELD<15, the 1-year survival rate is lower in patients receiving transplantation compared to those who were not transplanted.[18] Consequently, a MELD score of ≥15 is recommended for listing patients with end-stage liver disease.[26] The main advantage of the MELD model compared to the Child-Pugh class is the fact that only objective variables are used for its calculation and the lack of an upper limit for disease severity. Limitations include the need for computation, making it less user-friendly than the Child-Pugh score in daily clinical practice, and the lack of well-defined subcategories to assess individual mortality risk.[19] Modifications of the MELD score (ie, MELD-Na,[27 28] integrated MELD,[29] δ MELD[30]) have been proposed in recent years aiming to improve the predictive power of MELD.

Finally, considering the distinct prognosis of patients with compensated and decompensated liver cirrhosis, a four-stage clinical classification was proposed[14] and subsequently modified into a five-stage (2 stages in compensated and 3 stages in decompensated cirrhosis) system[31 32] (table 2): stage 1, compensated cirrhosis without varices; stage 2, compensated with varices; stage 3, bleeding without other disease complications; stage 4, first non-bleeding decompensating event (ie, ascites, jaundice, encephalopathy); stage 5, >1 decompensating event. The 1-year and 5-year mortality rates for each stage are 1.5% and 1.5% (stage 1), 2% and 10% (stage 2), 10% and 20% (stage 3), 21% and 30% (stage 4), and 27% and 88% (stage 5).[31 32] Notably, the very low probability of death (14%) before decompensation for compensated patients[31] supports the course of cirrhosis

Table 1 Child-Pugh score

Variable	Points 1	2	3
Encephalopathy	None	Stage I–II	Stage III–IV
Ascites	Absent	Controlled	Refractory
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/L)	>35	28–35	<28
Prothrombin time (seconds)	<4	4–6	>6
Sum of points	5–6	7–9	10–15
Stage	A	B	C
1-year survival rate (%)	95	80	44

Table 2 Clinical stages of liver cirrhosis

Stage	Definition	5-year mortality rate (%)
Compensated stages		
1	No varices	1.5
2	Varices	10
Decompensated stages		
3	Bleeding, no other decompensating event	20
4	Ascites, jaundice or encephalopathy	30
5	>1 decompensating event	88

to be considered as a progression across different prognostic stages.[33] However, an independent and prospective evaluation of this classification is required.

PRIMARY LIVER CANCER AND LIVER CIRRHOSIS

Hepatocellular carcinoma

Staging and liver function

HCC is the most common primary liver cancer and the second most common cause of cancer-related mortality globally.[1 34] Importantly, HCC usually develops in patients with underlying liver cirrhosis.[4 35] Hence, unlike in most other solid malignancies, the prognosis of patients is not only determined by the cancer itself but also by the degree of underlying liver cirrhosis[4 36 37] and its complications including portal hypertension, ascites, and life-threatening bleeding events from gastro-oesophageal varices.[38] Additionally, underlying liver cirrhosis further limits the applicability of certain treatment modalities since some standard therapies are a strain for the patients (eg, resection) or cause collateral damage to the non-cancerous liver tissue (eg, transarterial chemoembolisation (TACE)) and thereby potentially further aggravate liver dysfunction.[4 39 40] Taking these facts into account, a staging classification for HCC should consider both, prognostic relevant tumour characteristics and variables describing liver function, and ideally assign treatment modalities to each prognostic subclass.[4] Several prognostic classifications and staging systems for HCC have been proposed in the past[36 41–48] but only two (Barcelona-Liver Cancer (BCLC) staging system, Chinese University Prognotic Index (CUPI) score)[42 44 45] include all three prognostic categories (tumor extent, liver function, general condition) and only the BCLC system allocates evidence-based treatment strategies to each of the five resulting subclasses.[42 45] Consequently, the European as well as the American liver association endorsed the BCLC staging classification and treatment algorithm in their HCC management guidelines[4 49] and it became one of the most widely used classifications and treatment algorithms for HCC. Here, we focus on the influence of the severity of the underlying liver dysfunction on treatment allocation and prognosis rather than discussing the standard treatment of HCC according to guidelines in detail which can be found elsewhere.[4 49]

Liver function influences treatment decisions and prognosis

According to the current version of the BCLC algorithm, treatment allocation in HCC still depends on the severity of the underlying liver cirrhosis graded according to Child-Pugh class.[4 42 45 49] However, many experts in the field criticise the use of the Child-Pugh stage in HCC management since usually only the three gross categories A/B/C are used for staging while fine but prognostically relevant increments within one class (eg, Child-Pugh B, 7 vs 8–9 points)[50 51] are not considered. A proposed subclassification for patients with intermediate stage HCC already addresses this issue and uses Child-Pugh points instead of the Child-Pugh categories to assign patients to different prognostic subclasses[52] and a new score to assess liver function in patients with HCC has been proposed recently.[53] Based on the 2 serum parameters albumin (liver synthesis) and bilirubin (excretory function of liver) the authors developed the so-called 'Albumin-Bilirubin (ALBI) grade' that performs similar to the Child-Pugh score and could even reveal two prognostic classes within Child-Pugh class A patients. According to the authors its objectivity and simplicity might facilitate the assessment of liver function in patients with HCC and might improve patient selection for clinical trials.[53] However, prospective external validation is still required.

Resection

Hepatic resection is the first-line treatment for patients with solitary tumours and very well-preserved liver function (Child-Pugh A).[4] In cirrhotic patients, perioperative mortality and blood transfusion requirements should not exceed 2–3% and 10%, respectively.[4 54–57] This requires careful selection of candidates to avoid life-threatening surgery-related complications and necessitates an adequate assessment of liver function.[4 58] Since determination of the Child-Pugh stage is only a rough estimation of liver function some current guidelines recommend determination of indocyanine green retention rate at 15 min (ICGR15) or assessment of the severity of portal hypertension.[4 49 59 60] An ICGR15 cut-off value of ≤14% is generally used for suitability for major hepatic resection but may be extended to 15–20% if the estimated remnant liver volume is sufficient.[61] Hepatic venous pressure gradient (HVPG) measurement with a balloon catheter via hepatic vein catheterisation is the gold standard technique to assess the severity of portal hypertension and represents an equivalent of portal pressure in patients with liver cirrhosis.[62–64] HVPG values of ≥10 mm Hg represent clinically significant portal hypertension (CSPH).[62] Additionally, CSPH can also be confirmed by surrogate markers including gastro-oesophageal varices and platelet count below 100×10^9/L associated with splenomegaly.[65] Patients with absence of CSPH and normal serum bilirubin levels can achieve 5-year survival rates of around 70% after resection while it is about 50% for those with CSPH and even worse for individuals with CSPH and elevated bilirubin.[54 66] A recently published systematic review and meta-analysis reported that CSPH evaluated by any method significantly increased the risk of 3-year and 5-year mortality and of clinical decompensation after resection for HCC and therefore represents a major negative prognostic factor.[67]

Hence, current Western guidelines recommend resection only in patients with well-preserved liver function, defined as normal serum bilirubin levels with either HVPG ≤10 mm Hg or platelet count $\geq100\times10^9$/L.[4] By following these strict criteria and requirements

resection can be applied to only 5–10% of all patients with HCC.[58] Application of such strict selection criteria is largely dependent on good alternative treatment options, in particular orthotopic liver transplantation or a lesion amenable to local ablation. In the absence of such options and with only palliative treatment options left selection criteria for resection will be more liberal. Whether these strict criteria may also safely be expanded despite the availability of other curative options is currently unclear and should be evaluated in clinical trials considering other features of portal hypertension (eg, size of varices, history of bleeding) as well as the extent of hepatic resection.

Local ablation

Patients with tumours less than 3 cm (or maybe even up to 5 cm) and Child-Pugh stage A or B who are not suitable for hepatic resection are candidates for local image-guided tumour ablation.[4 49 58] Radiofrequency ablation is recommended in most cases since it is more effective than percutaneous ethanol injection in terms of local disease control and survival but shows a higher rate of major complications.[4 68–71] Similar to hepatic resection, severity of underlying liver dysfunction (Child-Pugh A vs Child-Pugh B) represents a main prognostic factor in patients undergoing local tumour ablation[72–75] but differently from resection, more advanced liver dysfunction does not represent a contraindication.

Liver transplantation

Liver transplantation is recommended for patients with small tumours and advanced liver function impairment. Transplantation is the only treatment modality that can simultaneously cure both, the tumour as well as the underlying liver cirrhosis, and the success of treatment is not affected by the severity of liver dysfunction.[4 58] According to the landmark paper published by Mazzaferro *et al*[76] patients with single tumours ≤5 cm or up to three tumours ≤3 cm, without vascular invasion or extrahepatic metastases are the best candidates and can achieve survival rates comparable to those of patients transplanted for non-malignant indications.[77] Consequently, the so-called 'Milan criteria' were incorporated in the European and American guidelines for HCC management and liver transplantation.[4 42 49 78]

Transarterial chemoembolisation

TACE is the first treatment choice for patient with compensated liver disease and large or multifocal HCC without vascular invasion or extrahepatic spread.[4] Contraindications for TACE have been reviewed elsewhere.[79 80] Absolute contraindications related to liver cirrhosis include decompensated status (Child-Pugh score >8,) and impaired portal-venous blood flow (thrombosis, hepatofugal blood flow), while untreated oesophageal varices with high bleeding risk represent a relative contraindication for TACE.[80] Since the target population for TACE represents a very heterogeneous patient population and the extent of tumour burden and liver function significantly impact the outcome of TACE[52] careful patient selection is inevitable. Several concepts, mainly based on tumour variables and liver function, aiming to facilitate the decision-making process have been proposed recently.[52 81 82] Not surprisingly, they demonstrate better survival outcomes after TACE for patients with initially well-preserved liver function.[52 81 82] Retreatment with TACE might be necessary in patients without complete response after the first TACE and highly depends on the liver function reserve and the liver damage induced by the previous TACE. The Assessment for Retreatment with TACE (ART) score was developed based on radiological tumour response and impairment of liver function (Child-Pugh score and serum aspartate aminotransferase (AST) increase) in order to facilitate the selection of patients who might benefit from repeated TACE treatment.[83 84] The authors reported that even discrete subclinical deterioration of liver function negatively impacted survival (median OS of the 2 prognostic subgroups, 23.7 vs 6.6 months) and was significantly associated with major adverse events.[83 84] Hence, optimal patient selection at baseline and before retreatment with TACE is crucial for minimising patient harm and the overall success of TACE and depends not only on tumour variables but also on the degree of hepatic dysfunction.[80] Regarding TACE technique, TACE with drug-eluting beads showed less liver toxicity and systemic side effects compared to conventional TACE[85] and might therefore be the better choice for patients with more advanced liver dysfunction (compensated Child-Pugh B). Superselective embolisation is recommended to minimise the ischaemic damage to the non-cancerous liver tissue in order to reduce the risk of treatment-induced liver failure.[4]

Sorafenib and best supportive care

The multikinase inhibitor sorafenib is the first systemic treatment that demonstrated a survival benefit in two randomised controlled phase III trials over placebo[86 87] and became the standard therapy for patients with advanced HCC (tumour symptoms, extrahepatic metastases, vascular invasion).[4] Both studies included almost exclusively patients with well-preserved liver function (Child-Pugh A), a common practice in HCC trials in order to avoid the potential masking of a treatment-related antitumour effect by death from underlying cirrhosis.[88] Hence, several groups have evaluated sorafenib in the setting of more advanced liver cirrhosis and identified the Child-Pugh stage as one of the strongest prognostic variable in patients with advanced HCC treated with sorafenib.[50 51 89–99] Results from the final analysis of the European subset of the GIDEON trial (Global Investigation of therapeutic Decisions in hepatocellular carcinoma and Of its treatment with sorafeNib), a global prospective non-interventional phase IV observational study, confirmed the prognostic role of Child-Pugh stage in a cohort of 1113 patients (median survival for

Child-Pugh A/B/C, 15.0/4.9/1.5 months).[100] While current guidelines recommend sorafenib for patients with advanced HCC and Child-Pugh class A, the use of sorafenib in the very heterogeneous (compensated vs decompensated) group of Child-Pugh B patients is still a matter of debate due to the lack of randomised and controlled prospective data.[4 101] In a retrospective analysis, baseline aspartate aminotransferase serum level, a parameter representing ongoing hepatocellular damage, was identified as a strong prognostic factor and could identify patients who were more likely to derive a clinical meaningful benefit from sorafenib treatment within the Child-Pugh B population.[94] The ongoing BOOST phase III study (NCT01405573), comparing overall survival with sorafenib versus best supportive care in 320 patients with HCC and impaired liver function (Child-Pugh B), will generate missing data to facilitate the proposal of clear recommendations for clinicians.

Notably, several preclinical[102–106] as well as small clinical pilot studies[107–109] suggest that sorafenib might also have beneficial effects on the portal hypertensive syndrome. Hence, the improvement of survival in patients with HCC treated with sorafenib might not only result from the antitumor effect alone but also from an improvement of the portal hypertensive syndrome.[104] So far, the grade of evidence is low and prospective randomised controlled trials investigating the effect of (low-dose) sorafenib on portal hypertension are needed before firm conclusions can be drawn.

Finally, recommendations for Child-Pugh C patients are clearly defined and suggest only best supportive care for patients with tumours beyond transplantation criteria due to their dismal prognosis of less than 3 months even if on sorafenib.[4]

Treatment of the underlying liver disease and portal hypertension

A large proportion of patients with HCC dies from complications of liver cirrhosis and portal hypertension (ie, gastrointestinal bleeding, infections, renal failure) rather than from clearly tumour-related causes.[110] Hence, not only effective antitumour treatment but also adequate evaluation and treatment of portal hypertension can reduce liver disease-related mortality.[111 112] Consequently, the evaluation and management of portal hypertension including screening for varices and medical treatment or/and endoscopic ligation if necessary[111 112] should be integral part of HCC management.

Additionally, management of modifiable factors and treatment of the underlying liver disease (ie, viral hepatitis or alcohol) has potential to improve the outcome of patients with HCC, especially in the curative therapeutic setting.[113–116] Shih *et al*[116] observed in a large prospective cohort study that continuing alcohol abuse had deleterious effects on HCC survival while cessation of drinking reduced HCC-specific mortality.

Several studies have shown that sustained hepatitis B virus (HBV) viraemia is associated with an increased risk of recurrence after surgical therapy,[117 118] while antiviral treatment can improve the outcome of patients undergoing resection for HCC.[115 119–121] A meta-analysis has shown that interferon therapy for chronic hepatitis C virus (HCV) improves the prognosis of patients with HCC after local ablation or resection of HCC.[122] Although specific data are lacking one could speculate that the higher rate of sustained virological response (SVR) achieved with the new interferon-free anti-HCV regimens might translate into an even more reduced recurrence rate following surgical or ablative HCC treatment. This in turn could finally lower the need for liver transplantation for HCV-associated HCC.[114] To prevent recurrent HBV infection after liver transplantation current guidelines recommend therapy with a potent nucleoside/nucleotide analogue (NA) with a high barrier to resistance for all HBsAg-positive patients to achieve the lowest possible level of HBV DNA before transplantation for end-stage liver disease or HCC.[113 123] After liver transplantation, the combination of hepatitis B immunoglobulin (HBIG) and a potent NA can effectively reduce HBV recurrence to less than 10% in liver transplant recipients[113 124] and dependent on HBV risk-stratification, HBIG can be discontinued in the long run in a sizable fraction of patients without an increase in recurrence rate.[125] For HCV patients awaiting liver transplantation or patients with post-transplant recurrence of HCV, current guidelines recommend antiviral treatment with an interferon-free regimen.[114] In general, antiviral treatment is not recommended in patients with limited life expectancy due to non-liver related comorbidities including cancer.[114]

Intrahepatic cholangiocarcinoma

Risk factors and staging

Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary liver cancer and shows increasing incidence rates over the past decades globally.[126–129] Among numerous risk factors described for iCCA[130] many are similar to those reported for HCC (ie, cirrhosis, chronic hepatitis B or C, alcohol)[131] although their prevalence is much lower in iCCA and the majority of iCCA develops sporadically in patients presenting with none of the known risk factors.[129 132] Hence, unlike for HCC, which mostly develops in patients with underlying liver disease/cirrhosis,[4 35 58] current guidelines for iCCA[5] recommend using the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICCA) staging manual[48 133] for treatment decisions which only considers prognostic tumour characteristics but no variables describing liver function. Notably, several proposed staging systems for iCCA are based on postsurgical patient cohorts[48 133–137] since surgical resection is the treatment of choice for patients with iCCA and individuals with advanced liver dysfunction are excluded from surgery anyway.[5]

The impact of liver function on treatment allocation and prognosis

Although the staging classification for iCCA only includes variables representing tumour extent several treatment modalities require prior evaluation of liver function.

Resection

Surgical resection is the standard treatment for patients with iCCA and is recommended for patients with a single tumour (curative intent) and might be performed as well in individuals with multinodular disease or vascular invasion (non-curative intent).[5] Patients with underlying liver cirrhosis should undergo careful assessment of liver function reserve according to the criteria suggested for HCC (as mentioned above).[4 5] As expected, the presence of liver cirrhosis is a negative prognostic factor in patients resected for iCCA.[138–140]

Liver transplantation

Liver transplantation is not recommended as a standard treatment for iCCA since survival rates, derived from heterogeneous and often small patient populations,[141–146] were markedly below those reported for cirrhotic patients undergoing transplantation.[147] A recently published retrospective cohort multicenter study reported an excellent 5-year survival rate of 73% for cirrhotic patients with single iCCA ≤2 cm. Given the small sample size (only 8 of 29 patients had iCCA ≤2 cm) and the retrospective nature of the study these results require further confirmation though.[148]

Locoregional treatment

Locoregional therapies (ie, TACE, radiofrequency ablation, radioembolisation, radiation) can be considered as an alternative treatment option in patients not suitable for surgery.[5 149] Since most data were derived from retrospective, non-randomised studies that included different types of biliary tract cancer and had a small sample size, current guidelines do not recommend these treatment modalities as standard therapies for iCCA.[5] However, TACE has shown some antitumor activity in rather small and mostly retrospective studies.[150–157] Similar to HCC, careful patient selection with regard to parameters recommended for HCC (ie, liver function, contraindications, tumour extent, general health condition)[4 80] is inevitable for the overall success of TACE, even though distinct data for iCCA are scarce.

Radioembolisation with yttrium-90 microspheres represents another transarterial treatment modality currently under investigation for the use in HCC but has also been applied to patients with iCCA.[5] A recently published review and pooled analysis[158] reported similar survival rates to patients treated with systemic chemotherapy or TACE. The rate of liver-related complications was low and included liver enzyme elevation, ascites and acute/chronic radiation hepatitis.[158]

Radiofrequency ablation can be considered for small tumours <3 cm if hepatic resection is contraindicated (eg, advanced liver cirrhosis or clinical significant portal hypertension),[4 5] even though survival results are worse compared to HCC.[159–163] Major liver-related complications, including liver abscess or biliary strictures, were rarely observed.[164]

External-beam radiation therapy (EBRT) has shown some antitumor effect in iCCA and might be useful as a palliative treatment option to relieve pain and jaundice.[5 165–169] Since a whole-liver dose of more than 40 Gy is frequently associated with severe adverse events, including life-threatening radiation-related liver disease, only patients with small tumours, enabling radiation therapy to a small liver area, are amenable to EBRT. The development of stereotactic body radiotherapy, which allows high dose of radiation in the tumour while the surrounding tissue only receives a fraction of the dose, has largely improved this problem.[149 170] A recently published retrospective study reported that a biological equivalent dose of >80.5 Gy seemed to be an ablative dose of radiation therapy for large iCCA and can achieve survival rates comparable to resection. No case of radiation-induced liver disease was reported.[171] However, baseline liver function is an important factor for patient selection here as well.[172]

Chemotherapy

Based on data derived from studies conducted in patients with advanced biliary tract cancer[173–175] the combination of cisplatin plus gemcitabine became the chemotherapy practice standard for iCCA, even though, given the limited data available on iCCA, current guidelines do not recommend this regimen as a standard of care for iCCA.[5] Gemcitabine commonly causes transient elevation of transaminases, but liver failure is rare. Dose reduction is recommended in patients with significant underlying liver disease.[176 177] Cisplatin can induce a transient increase of transaminases, especially at higher doses, as well as steatosis and cholestasis, which are rare and usually reversible though.[178]

Management of the underlying liver disease

Similar to HCC, patients with underlying liver cirrhosis should be screened for portal hypertension and its complications and undergo adequate management if present.[111 112] Additionally, modifiable causal factors (ie, alcohol, hepatotoxic drugs) should be managed adequately and decisions regarding treatment of the underlying liver disease (ie, viral hepatitis) should be based on the liver disease-related and cancer-related prognosis.[114 179] A recently published retrospective study[180] reported that HCV infection was a negative prognostic factor in patients undergoing curative resection for iCCA. Notably, five HCC-related deaths occurred in patients with underlying HCV infection while no HCC-related death was observed in individuals without HCV infection.[180] However, due to a lack of high-quality

data it can only be hypothesised that antiviral treatment after curative resection for iCCA might be beneficial by preventing progression of liver disease and eventually by reducing the incidence of metachronous HCC.

Non-hepatic cancer and liver cirrhosis

General

Cancer and liver cirrhosis represent major health burdens and account for about 1.75 million and 170 000 deaths per year in Europe, respectively.[2 181] Given the high prevalence of each disease[1 2] and the fact that common habits among the general population like tobacco, alcohol abuse and the metabolic syndrome represent risk factors for both, cancer and cirrhosis,[7–12] one can assume that a remarkable number of patients with solid tumours concomitantly suffer from liver cirrhosis.[179 182] Additionally, patients with liver cirrhosis not only bear a higher risk for liver cancer but also for extrahepatic malignancies compared to the general population.[6] A recently published England-based nationwide cohort study reported that the crude mortality rates per 100 person-years for HCC and non-liver cancer in patients with liver cirrhosis were 0.69 and 2.48, respectively.[183]

Anticancer treatment and liver cirrhosis

The survival of patients with liver cirrhosis varies according to the severity of liver dysfunction and is significantly shorter in patients presenting with decompensated disease with a 1-year mortality rate between 20% and 57%.[14] While the prognosis of patients with cancer and very advanced (decompensated, Child-Pugh C) liver cirrhosis is mostly determined by the liver disease patients with compensated disease (median survival based on liver function impairment: >12 years[14]) rather die from tumour-related complications and therefore might derive a clinically relevant benefit from anticancer treatment. These considerations have to be taken into account when decisions about the possible initiation of anticancer treatment are made.

Since clinical studies usually exclude patients with underlying liver cirrhosis, only little is known about anticancer treatment in patients with non-hepatic cancer and concomitant liver cirrhosis. Most data were derived from trials with small patient numbers and the study design was mostly retrospective.[179 184]

Surgery

Surgical treatment is frequently indicated in patients with cancer especially at early tumour stages and often the only curative treatment option.[7 185–187] In general, the severity of liver dysfunction is a main prognostic factor in patients with liver cirrhosis undergoing surgery.[188] The mortality rates increase with more advanced liver cirrhosis and were 10%, 30–31% and 76–82% for Child-Pugh stage A, B and C after major abdominal surgery.[188–190] Similarly, the MELD score also predicts mortality after surgery in patients with liver cirrhosis and represents probably the most precise predictor of perioperative mortality.[188 191 192] In a large retrospective study including 772 patients with cirrhosis who underwent cardiovascular, orthopaedic or abdominal surgery 30-day postoperative mortality rates of 5.7%, 10.3%, 25.4%, 44.0%, 53.8% and 90.0% were observed for MELD scores ≤7, 8–11, 12–15, 16–20, 21–25 and ≥26.[192] Additionally, a retrospective study evaluating 140 patients with cirrhosis who underwent surgery reported approximately a 1% increase in mortality with each integer increase in MELD between MELD scores of 5 and 20 and approximately a 2% increase in mortality for each one-point increase in MELD above 20.[191]

In gastric cancer, liver cirrhosis was an independent risk factor for postdischarge morbidity after radical gastrectomy[193] and patients with more advanced (Child-Pugh B-C) cirrhosis had a significantly higher postoperative complication rate (72.7% vs 30.4%) and mortality rate (27.2% vs 4.3%) as well as a shorter long-term survival (5-year survival rate, 11% vs 66%) after curative surgery than patients at Child-Pugh stage A.[194] A recently published retrospective multicenter study reported that patients with Child-Pugh A liver cirrhosis who underwent pancreaticoduodenectomy for pancreatic cancer had a higher complication rate than matched non-cirrhotics (79% vs 43%); all Child-Pugh B patients (n=11/11) and all participants with preoperative portal hypertension (n=6/6) experienced postoperative complications.[195] In head and neck cancer, patients with more advanced liver cirrhosis (Child-Pugh B-C) had a higher complication rate after tumour resection and microsurgical free tissue transfer and MELD was an independent predictor for postoperative morbidity and mortality.[196–198] In patients undergoing surgery for colorectal carcinoma (CRC), the 30-day mortality was higher in individuals with cirrhosis compared to the general population (24.1% vs 8.7) with a relative risk of 2.59 (95% CI 1.86 to 3.61).[199] In another retrospective study including only CRC patients with liver cirrhosis, the degree of liver function impairment (Child-Pugh stage A vs B-C) was significantly associated with perioperative mortality and long-term survival (5-year survival rate, 52% vs 23%) while tumour variables ('Tumor-Node-Metastasis' classification) had no prognostic implication in this cohort.[200]

In conclusion and as a general consensus, elective surgery is well tolerated in patients with Child-Pugh A cirrhosis, acceptable for Child-Pugh stage B after careful preoperative preparation, and contraindicated in Child-Pugh stage B patients undergoing major hepatic resection or cardiac surgery as well as in individuals with Child-Pugh C cirrhosis.[188 201] The Child-Pugh score and the MELD score should be used complementary to estimate the 30-day and 90-day postoperative mortality in patients with cirrhosis undergoing surgery.[201]

Resection of liver metastases is a common practice in some malignancies including colorectal cancer.[202 203] Notably, the risk of developing liver metastases from colorectal cancer seems to be lower in patients with

underlying liver cirrhosis.[204 205] Adequate assessment of liver function and portal hypertension is inevitable before surgery.[4 188] As recommended for HCC, liver resection should only be performed in patients without CSPH.[4] Adequate liver remnant with vascular inflow and outflow preservation is crucial and, if necessary, can be achieved by advanced techniques such as portal and/or hepatic venous embolisation or two-stage hepatectomy.[202 206 207] Patients with underlying liver cirrhosis benefit the most from portal vein embolisation.[207] Additionally, it was shown that a longer interval between preoperative chemotherapy and liver resection is associated with a reduced risk of postoperative complications in patients with colorectal liver metastases.[208–210] Based on the results from the EORTC 40983 study, an interval of 5 weeks was recommended to balance the risk of postsurgical complications on the one hand and tumour progression due to treatment delay on the other hand.[211]

Chemotherapy

Cytotoxic chemotherapy is another mainstay in cancer treatment. Several chemotherapeutic agents can cause liver toxicity of varying degree ranging from mild transient elevation of liver enzymes to severe or even fatal hepatic failure.[184 212–214] The liver itself is fundamentally important in drug metabolism (ie, activation, inactivation, excretion) and patients with abnormal drug metabolism have an increased risk of experiencing severe hematological as well as non-hematological adverse events.[184 212] Hence, caution and carful assessment and monitoring of liver function before and during therapy are inevitable in order to improve the success of anticancer treatment.[179 184] The answer to the critical question whether a patient with liver cirrhosis should be treated with chemotherapy or not has to take into account the liver-related as well as the tumour-related prognosis and can be considered as 'yes' if the definite life expectancy is mainly determined by the cancer and exceeds more than 3 months.[179] An interdisciplinary approach involving oncologists and hepatologists is indispensable for providing optimal management and patient care.[179]

Cabibbo *et al*[179] recently proposed a decision algorithm for patients with non-hepatic cancer and liver cirrhosis. The authors recommend to consider cytotoxic chemotherapy in patients with compensated (Child-Pugh score ≤7 points, no clinically relevant ascites) cirrhosis. Individuals at decompensated stage (Child-Pugh >7 or clinically relevant ascites) should rather receive adequate management of decompensated cirrhosis and best supportive care; however, cytoreductive treatment might be considered in patients with space-occupying lesions in high-risk areas (ie, intracranial or mediastinal).[179]

Although drug toxicity and elimination is believed to be only moderately influenced by underlying mild to moderate liver function impairment (other than in Child-Pugh stage C)[184 215] certain chemotherapy-associated side effects may have more relevance in patients with underlying liver cirrhosis.[179] For instance, pancytopenia due to splenic pooling and sequestration of corpuscular blood components secondary to portal hypertension[216] might aggravate the effects of chemotherapy-induced bone marrow suppression.[179] Additionally, cancer and cytotoxic chemotherapy as well as liver cirrhosis frequently come along with coagulation disorders.[217] Consequently, the risk of developing thrombosis in the portal or mesenteric veins, which is already elevated in patients with cirrhosis due to reduced portal blood flow and hypercoagulability,[218] might be further increased by the hypercoagulable state induced by cancer and several chemotherapeutic agents.[217] Certain other anticancer drugs like vascular endothelial growth factor inhibitors (ie, bevacizumab) are associated with bleeding complication[219] and might further increase the risk of variceal haemorrhage in patients with liver cirrhosis.[220] Thus, adequate management of portal hypertension (screening for varices and band ligation or β-blocker treatment if necessary) is inevitable before treatment start.[111 112]

Data on the use of cytotoxic chemotherapy in patients with liver cirrhosis are scarce since liver cirrhosis is usually an exclusion criterion in most clinical cancer trials. Thus, current knowledge is low-grade evidence and mostly obtained from small retrospective or phase I trials and from studies testing agents in patients with HCC and underlying cirrhosis. Clear guidelines are lacking and most decisions are made empirically in clinical practice.[179] Dose modification recommendations for the use of certain anticancer agents in patients with underlying liver function impairment have been proposed in several reports or can be found in the prescribing information, for instance for vincristine, vinblastine and vinorelbine,[221–223] irinotecan,[222 224–226] procarbazine,[222] etoposide,[222 227] paclitaxel and docetaxel,[228–230] doxorubicine,[222 231] epirubicine,[222 232] daunorubicin,[222] gemcitabine,[233 234] imatinib,[235 236] erlotinib,[237 238] temsirolimus and everolimus,[239] pazopanib,[240] lapatinib, bortezomib, bosutinib, ixabepilone, nilotinib and panobinostat.

A detailed review of the literature about hepatotoxicity of chemotherapy and administration of cytotoxic agents with or without dose modification in patients with impaired liver function can be found elsewhere.[179 184 212–214 222 241]

Management of liver disease

Careful evaluation of the aetiology and severity of liver cirrhosis is necessary prior to initiation of anticancer treatment. Modifiable causal factors (eg, alcohol, liver toxins including drugs with known hepatotoxicity, diabetes) should be corrected in order to prevent worsening of the liver disease. Additionally, patients should be screened for portal hypertension and its complications and undergo adequate management if present,[111 112] especially those patients whose prognosis is mainly

determined by the liver disease (ie, very advanced/decompensated cirrhosis, potential curative cancer treatment).[179]

Reactivation of viral hepatitis

In general, reactivation of viral hepatitis during chemotherapy can be divided into three different stages.[242–247] First, chemotherapy-induced immunosuppression facilitates viral replication by reducing immune response that controls viral infection. The second stage is characterised by an 'immunological rebound' after cessation of chemotherapy, characterised by restored immune function and rapid destruction of viral-infected hepatocytes leading to increased liver inflammation and hepatocellular injury. The 'recovery phase' represents the final stage and is characterised by normalisation of viral markers and clinical symptoms of hepatitis.[242–247]

Reactivation of HBV infection during chemotherapy can lead to fulminant hepatitis resulting in liver failure or even death (mortality rate, 5–52%); the risk is especially increased in patients receiving rituximab and/or high-dose steroids.[243 246 248–254] HBV reactivation is defined by an abrupt increase in HBV DNA levels (>1 $\log_{10}$ copies/mL higher than before treatment start or absolute increase >6 $\log_{10}$ copies/mL) among patients with positive hepatitis B surface antigen (HBsAg) or the reappearance of HBV DNA in patients with resolved infection and is usually accompanied by an elevation of serum liver aminotransferases (hepatitis).[246 253 255] All patients should be screened for HBsAg and hepatitis B core antibodies (anti-HBc) before initiation of treatment.[113 179 212 252 254 256] HBV seronegative patients should undergo vaccination.[113 246] table 3 summarises treatment indications before chemotherapy as recommended by the EASL guidelines for HBV management.[113]

HBsAg-positive patients (regardless of HBV DNA levels) and HBsAg-negative, anti-HBc positive individuals with detectable serum HBV DNA should be treated with a nucleoside analogue during anticancer therapy and for at least 12 months after the last cycle of chemotherapy.[113 246] Lamivudine might be sufficient in candidates with low HBV DNA levels (<2000 IU/mL) and short duration of immunosuppression[113 246 257 258] while nucleoside analogues with higher potency and barrier to resistance (ie, entecavir, tenofovir) are recommended for patients with high viral load and/or long-lasting chemotherapeutic therapy.[113 246]

HBsAg-negative, anti-HBc positive candidates with undetectable serum HBV DNA levels should be monitored carefully during chemotherapy with alanine aminotransferase (ALT) and HBV DNA testing (every 1–3 months) and undergo antiviral treatment with a nucleoside analogue if HBV reactivation occurs.[113 246] It was recently reported that high titres of anti-HBs were protective for HBV reactivation during rituximab-based chemotherapy.[259] Prophylaxis should be given in special indications (ie, bone marrow or stem cell transplantation, rituximab and/or combined regimens for hematological diseases).[113 246 249 260–263]

Reactivation of HCV infection can also occur during chemotherapy[245 264 265] but is less common and usually less severe than HBV reactivation.[246 266–268] However, mortality rates seem to be similar between HCV-infected and HBV-infected patients once severe hepatitis due to viral reactivation occurs.[246 269 270] HCV reactivation is characterised by an at least threefold increase in serum ALT levels not explained by other causes (ie, tumour infiltration of liver, hepatotoxic drugs, recent blood transfusions, other systemic infections except HCV) which can be accompanied by reappearance or abrupt increase of HCV RNA levels. In patients with chronic HCV infection an increase of HCV RNA of more than 1 $\log_{10}$ IU/mL might indicate HCV reactivation since these patients usually have stable RNA values (variations by about 0.5 $\log_{10}$ IU/).[246 271]

No specific prophylaxis is established for HCV patients undergoing chemotherapy.[114 246] Once chemotherapy is started, an individualised approach with close monitoring of serum ALT (every 1–2 weeks) and HCV RNA (every 4 weeds) until 3 months after treatment cessation is recommended. In patients with elevated ALT levels, viral reactivation should be confirmed by HCV RNA measurement (>1 $\log_{10}$ IU/mL compared to baseline). Discontinuation of chemotherapy should be considered if increasing ALT levels preclude its use.[246]

Table 3 Pre-emptive hepatitis B treatment before chemotherapy

HBsAg	Anti-HBc	HBV DNA	Recommendation
+	N/A	<2000 IU/mL	▶ Finite and short duration of CHT: lamivudine may suffice; ▶ Lengthy and repeated cycles of CHT: NA with higher potency and barrier to resistance, ie, tenofovir or entecavir
+	N/A	>2000 IU/mL	NA with higher potency and barrier to resistance, ie, tenofovir or entecavir
–	+	Undetectable	Close monitoring of ALT and HBV DNA (1–3 monthly), treat with NA on confirmation of HBV reactivation; consider prophylaxis in special indications, ie, bone marrow or stem cell transplantation, rituximab and/or combined regimens for hematological diseases
–	+	Detectable	Treat similarly to HBsAg+patients

ALT, alanine aminotransferase; anti-HBc, hepatitis B core antibodies; CHT, chemotherapy; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid; N/A, not applicable; NA, nucleoside analogues.

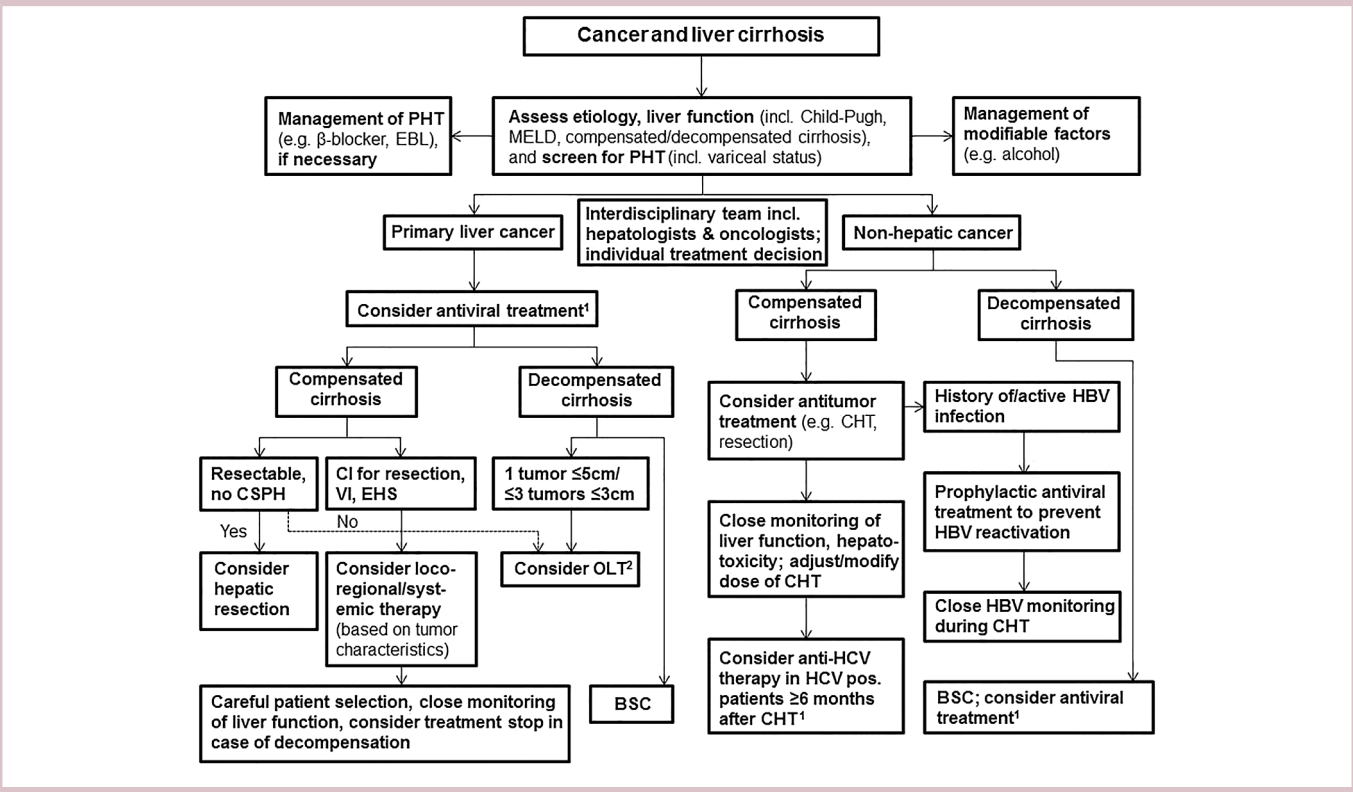

Figure 1 Proposal of a simplified treatment algorithm in patients with cancer and liver cirrhosis. [1] Both tumour- and liver-related prognosis should be taken into account. [2] Liver transplantation is not a standard treatment for intrahepatic cholangiocarcinoma. BSC, best supportive care; CHT, chemotherapy; CI, contraindication; CSPH, clinically significant portal hypertension; EBL, endoscopic band ligation; EHS, extrahepatic spread; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; OLT, orthotopic liver transplantation; PHT, portal hypertension; VI, vascular invasion.

Historically, anti-HCV agents such as interferon and ribavirin have been avoided during chemotherapy due to potential drug interactions and aggravation of hematological side effects.[179 246 272 273] Hence, management of HCV reactivation has traditionally been only supportive including dose reduction or cessation of chemotherapy or switching to an alternative chemotherapy regimen.[246 273] Borchardt and Torres[273] recently recommended to start HCV treatment in cancer survivors without evidence of metastatic disease not before 6 months after cancer remission. In general, antiviral treatment is not recommended in patients with limited life expectancy due to non-liver related comorbidities like cancer,[114] but survival for many cancers treated medically has improved so much that antiviral therapy might be warranted. The recent advances in HCV treatment including the development of the new, almost side effect-free direct-acting antivirals and the establishment of interferon-free regimens[114 274] may change the therapeutic approach to HCV infection in patients with cancer, depending on costs and drug-interaction profiles of available and future treatment regimens.

CONCLUSIONS

The degree of underlying liver cirrhosis significantly influences treatment decisions and prognosis of primary liver cancer and non-hepatic liver cancer. Adequate assessment of liver function and stage of cirrhosis prior to treatment initiation and close monitoring during anticancer treatment are inevitable. Patients with compensated liver cirrhosis, whose prognosis is mostly determined by the cancer, should be considered for antitumour treatment. In contrary, management of patients with decompensated stages should rather focus on liver cirrhosis and its complications since life expectancy is mainly influenced by the liver disease and antitumour treatment itself can further worsen liver function. In patients with underlying HBV infection antiviral treatment should be initiated prior to chemotherapy and close monitoring of liver function is recommended in patients with HCV infection. Figure 1 shows the proposal of a treatment algorithm for patients with cancer and liver cirrhosis. Since patients with liver cirrhosis are usually excluded from clinical trials only little is known about adequate dosing of chemotherapeutic agents in these patients. Future clinical trials investigating anticancer agents should start including patients with compensated cirrhosis in order to generate evidence-based dose modification recommendations in patients with liver cirrhosis.

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Funding This work was supported by an Erwin Schroedinger fellowship from the Austrian Science Fund (FWF; project number: J 3747-B28) to M. Pinter and two grants from the National Institutes of Health (NIH; grant numbers: P01 CA080124 and R01 DK103879).

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

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