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Research Article

Diagnosis, Prognosis & Therapy of Hepatocellular Carcinoma

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Abstract

Tumors are labeled to stratify patients concerning their survival prognosis and to pickand provide optimized therapeutic options at any tumor stage. For hepatocellular carcinoma (HCC) the Barcelona Clinic Liver most cancers (BCLC) type has been followed as the international general, which is recommended using both the Yankee association for the examination of Liver sicknesses (AASLD) and the ecu affiliation for the take a look at of the Liver (EASL) (table 1). The BCLC type considers several aspects of the sickness: the affected person's standard kingdom of health, the severity of the liver sickness, and the quantity of tumor spread (Llovet 1999) [1]. sufferers in levels, BCLC O and A have a significantly higher diagnosis than patients with advanced degrees of liver cancers (Mazzaferro 1996) [2] but roughly the Simplest 25% of patients with liver cancers are identified at an early stage. Each EASL (EASL 2012) [3] and AASLD guidelines provide tips concerning which therapy is perfect for patients at every stage of the BCLC class. unlike classification schemes in Different styles of malignancies, the BCLC class is especially useful because it's miles based on medical parameters – molecular characteristics cannot yet reliably assess The personal diagnosis of patients with HCC. The BCLC class appears to evaluate diagnosis less accurately in Asian sufferers, wherein hepatitis B is a triumphing motive of liver most cancers. An alternative type, the Hong Kong Liver Cancer Staging Machine (HKLC), has been proposed these days, which had a significantly better potential in Asian patients to differentiate subgroups with particular usual survival times (Yau 2014) [4]. Importantly HKLC identified subsets of sufferers with intermediate and advanced degrees of liver cancer, who would possibly benefit from extra-aggressive remedies (resection within the intermediate level, chemo embolization inside the advanced degree). Nonetheless to this point, the HKLC category is primarily based completely on retrospective records from Asian sufferers in a single middle and still awaits confirmation using prospectively managed studies and in non-Asian patients.

Keywords: diagnosis of hepatocellular carcinoma; surgical resection; hepatocellular carcinoma; liver transplantation; radiofrequency ablation; microwave ablation

Introduction

The Cancer of the Liver Italian Program (CLIP) has derived another widely used prognostic tool for HCC. The CLIP score combines features of macroscopic tumor morphology (uni modular versus multi-modular with limited extension < 50% versus massive with extension > 50%), serum alpha-fetoprotein (AFP <400 ng/mL versus >400 ng/mL), the Child-Pugh stage, and the presence of portal vein thrombosis to determine a prognostic a score ranging from 0 -6 (Anonymus 2000) [5]. Patients with advanced HCC and low serum levels of vascular endothelial growth factor (VEGF) or high levels of insulin-like growth factor, I (IGF-1) have better survival in each disease state than those with serum levels in the opposite range. Thus, VEGF and IGF-1 can be added to the CLIP score as an additional component referred to as V-CLIP or I-CLIP, respectively (Kaseb 2011a and 2011b) [6.7]. The latest prognostic classification Combines serum albumin and bilirubin alone (the ALBI score) and provides an easy to-use, objective and discriminatory method for assessing liver functions in patients with HCC. Its validity has been confirmed in geographically distinct cohorts of patients with HCC either undergoing liver surgery for localized disease and sorafenib treatment for advanced disease (Johnson 2015) [8].

Epidemiology

HCC constitutes the fifth most frequent form of cancer worldwide, and it holds second place in malignancy-related mortality (Jamal 2011) [9]. Incidence and death rates of HCC are steadily rising in most parts of the world (about 2-3% per year). It occurs two to six times more frequently in men than in women. The key risk for HCC is liver cirrhosis, approximately 80% of these are related to hepatitis B and C on a global

scale. Chronic hepatitis B is the major risk factor for developing HCC in Africa and Asia, while in the US, Europe, and Japan chronic hepatitis C, alcohol and nonalcoholic steatohepatitis (NASH) are leading causes of HCC. Eighty percent of liver cancers are found in cirrhotic livers, which themselves carry a high risk for HCC. Chronic carriers of hepatitis B virus (HBV) have a 100-fold increased risk as compared to a non-infected healthy reference population. Recent reports from Taiwan indicate a direct link between HBV viral loads and the risk of developing liver cancer within 10 years (Chen 2006, Iloeje 2006). [10,11] The risk of HCC is significantly increased once HBV DNA exceeds 2000 IU/mL irrespective of the degree of hepatic inflammation. Quantitative HBsAg ≥1000 IU/mL is a further biomarker of increased HCC risk in patients with low or intermediate levels of HBV-DNA (Tseng 2013) [12]. The risk to develop HCC is higher in infection with HBV genotype C than B and also in infection with genotype D than A. Co-infection with HCV and HDV and/or exposure to environmental toxins such as aflatoxins and the algal toxin microcystin in drinking water further increase the risk of HCC. Approximately 70 million people are infected with the hepatitis C virus worldwide, 20 to 30% of whom will develop liver cirrhosis, which carries a 3-5% annual risk of ultimately progressing to liver cancer. Unlike hepatitis B, a close relationship between HCV-RNA and the risk of developing HCC does not exist (Bralet 2000)[13] As a general rule patients will not develop liver cancer in chronic hepatitis C before their disease has progressed to advanced fibrosis And cirrhosis (Lok 2009)[14].It appears that the risk of HCV-induced HCC is related to The degree of inflammation and necrosis, while HBV-related HCC does not correlate Well with inflammation and seems rather involve the activation of specific oncogenes by the virus. Consumption of alcohol or tobacco enhances the risk of HCC (Donato 2002, Gelatti 2005) [15,16]. Beyond that, obesity (Calle 2003) [17] and Diabetes mellitus (Davila 2005) [18] must be considered pivotal risk factors that can independently lead to liver cancer in Western countries and result in 4- to 40-fold increased HCC rates among patients with chronic viral hepatitis (Starley 2010). In patients with steatohepatitis, liver cancer can occur before cirrhosis has developed. Importantly, the risk of HCC is substantially reduced in diabetic patients who are treated with metformin (Lai 2012) [19]. Finally, certain hereditary diseases such as Hemochromatosis and alpha1-antitrypsin deficiency predispose HCC. Also, genetic polymorphisms in the adiponectin gene (rs 738409 C>G), in the KIF1B gene (rs17401966), and the MICA gene (rs 2596542) seem to predispose patients with alcoholic and non-alcoholic fatty liver disease, chronic HBV, and HCV infection, respectively, to develop cirrhosis and HCC (Fallet 2011, Nischalke 2011, Trepo 2013, Zhang 2010, Kumar 2011). [20,21,22,23,24 Surveillance of patients at high risk and early HCC diagnosis Surveillance is cost-effective if the expected HCC risk exceeds 1.5% per year in hepatitis C and 0.2% per year in hepatitis B. Simple clinical scores have been developed in hepatitis B (e.g., the REACH-B score) and hepatitis C (e.g., the HALT-C score) to assess when HCC surveillance becomes cost-effective (Chen 2013, Yuen 2009, Lok 2009) [25]. Surveillance has to be based on ultrasound examination at 6 Month intervals. When 3- versus 6-month surveillance intervals were compared in a randomized study involving 1200 patients, there was no evidence that the shorter interval improved rates of early diagnosis and therapeutic outcomes. However, if patients with cirrhosis harbor nodular lesions, the 3-monthly control interval is preferred due to the high potential of malignancy and growth characteristics of such lesions (Yao 2006) [26]. Thus, nodules <1 cm, which usually are not HCC, should be monitored in 3–4-month intervals until they are proven to be stable or disappear (for up to 24 months). Nodules >1 cm should be evaluated with either 4-phase computed tomography (CT) or dynamic contrast-enhanced magnetic resonance imaging (MRI)as outlined in the section on diagnosis. Alpha-fetoprotein (AFP) has insufficient sensitivity and specificity and thus is no longer recommended for HCC surveillance. Des-gamma carboxy pro thrombin (DCP), glycosylated AFP (AFP-L3), and glypican-3 are being evaluated concerning HCC surveillance, and integrated as components of the GALAD score have outperformed ultrasound in a recent study suggesting that their combination with ultrasound might result in improved HCC surveillance of high risk patients (Yang 2019).[27] The consistent use Of ultrasound in patients with high risk for HCC enables us to diagnose carcinoma Early in 30% of patients who then have a reasonable chance of curative therapy. On The other hand, Caucasian patients with low or no HBV activity is at low risk for HCC, and surveillance is generally not recommended in such patients.

Diagnosis

patients who develop HCC generally have no symptoms other than those related to the underlying chronic liver disease. but, in sufferers with sudden hepatic decompensation which include ascites, jaundice, hepatic encephalopathy, or variceal bleeding regularly due to portal vein thrombosis there is an elevated chance of HCC. now and then sufferers increase paraneoplastic syndromes (hypoglycemia, erythrocytosis, hypercalcemia, intense watery diarrhea, dermatomyositis, and diverse types of pores and skin lesions), which aside from erythrocytosis bring in negative diagnosis (Luo 2002).Plasma micro-RNAs are currently below evaluation As biomarkers for the non-invasive diagnosis of HCC at any level (Borel 2012).[28] The prognosis of HCC is made by using detecting malignantly transformed hepatocytes in a liver biopsy or by using dynamic comparison-better radiological imaging techniques demonstrating severe arterial uptake followed using wash-out of evaluation in the not-on-time venous phases reflecting arterialized perfusion of the tumor. contrast-better ultrasound may falsely advise HCC in a few sufferers with cholangiocarcinoma, and it ought to no longer be used as the simplest diagnostic tool for HCC (Vilana 2010) [29]. nonetheless, novel diagnostic algorithms enable the prognosis of HCC in a cirrhotic liver without histopathology or connection with expanded tumor markers. The revised WHO classification distinguishes new specific subtypes of hepatocellular carcinoma (steatohepatitis, clean cell kind, macro trabecular huge, chromophobe fibrolamellar, scirrhous, neutrophil-wealthy, lymphocyte rich (WHO 2019) [30]. mainly, the distinction between a dysplastic nodule and early HCC poses a selected assignment for the pathologist. Staining for glycan-three, heat shock protein 70, and glutamine synthetase is counseled in this example and positivity for any two of these 3 markers confirm the presence of HCC (international working celebration 2009) [31]. Differentiation of HCC from cholangiocarcinoma might also require mobile-type precise markers consisting of keratin-7, keratin-19, or CA 19-9. The radiological prognosis of HCC uses the detection of hyper-vascularised nodular lesions. assessment-greater computed tomography (CT) or nuclear magnetic spin resonance tomography (MRI) is considered to be equal diagnostic gear and international consensus pointers be

given a diagnosis of HCC without histopathology if the patient with a nodular lesion in a cirrhotic liver reveals the following series of activities: within the arterial section, HCC complements more intensely than the surrounding liver, due to the fact arterial blood within the liver is diluted by way of venous blood from the portal venous circulation, whereas HCC includes simplest arterial blood. within the venous phase, HCC enhances much less than the liver, reflecting the reality that HCC does not have a portal venous blood supply and that the arterial blood flowing into the lesion now not includes evaluation. This phenomenon is named “washout”. within the delayed segment “washout” persists, and every so often HCC can only be detected in this section of a dynamic study. consequently, a four-phase dynamic has a look at is needed to reliably make a diagnosis of HCC (unenhanced, arterial, venous, and behind-schedule venous levels). comparison enhancement within the early arterial phase, which disappears within the past due venous section, is pretty particular for HCC. Diffusion-weighted imaging (DWI) in MRI displays water mobility in tissues, that are impeded in HCC tissue. hence HCC outcomes in signal hyperintensity within the tumor relative to the liver parenchyma. A current meta-analysis supplied evidence that DWI

blended with dynamic contrast-enhanced MRI performed significantly better than any of the two imaging techniques alone (Wu2013}{32} Hepatocyte-specific contrast agents such as graduate disodium and gadobenate dimeglumine are taken up by normal hepatocytes. Since most HCCs do not contain functional hepatocytes, signal hypointensity relative to the surrounding liver is observed in the hepatobiliary phase. As a consequence, hepatobiliary phase images are highly sensitive to HCC. However, this technique has only poor specificity (Bartollozzi 2013) [33]. Nodules with a hypo-intense signal in the hepatobiliary phase but without diagnostic features of HCC in the other phases may represent highly dysplastic nodules or early HCC and carry a high risk of progressing to conventional hyper vascular HCC. The current recommendations for the diagnosis of HCC are summarized in Figure 1. For lesions smaller than 1 cm, a detailed investigation is not recommended because most lesions will represent regenerative nodules rather than HCC. However, close follow-up in 3-month intervals should be offered using the same imaging technique that detected the lesion in the first place. For lesions larger than 1 cm, a guided biopsy of the lesion should be performed because the diagnostic accuracy of radiological procedures declines with smaller liver tumors, while high (>90%) diagnostic sensitivity and specificity are maintained by histological analysis of biopsy specimens (Serste 2012) [34]. Alternatively, either dynamic MRI or multi-detector CT scans can be performed. If radiological findings are characteristic of HCC as described above, a firm diagnosis of HCC can be made, and no further steps are necessary. Contrast-enhanced CT and MRI exhibit excellent diagnostic sensitivity and specificity if the rules regarding early hypervascularity and washout are strictly applied. The presence of arterial hyper vascularisation alone is not sufficient for a diagnosis of HCC, which requires the presence of venous washout as an essential second diagnostic component. In equivocal situations, the diagnosis must be clarified by biopsies, which may have to be repeated within a short period.

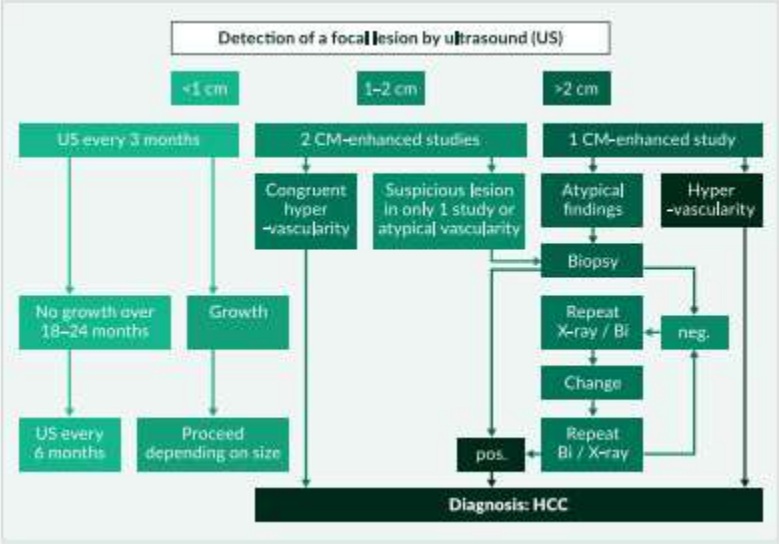

Figure Diagnostic algorithm for the diagnosis of hepatocellular carcinoma depending on tumour size Radiological assessment of treatment responses should not be based on tumor size alone but apply modified Response Evaluation Criteria in Solid Tumours (mRECIST) (Lencioni 2010) [35]. High-quality arterial-phase imaging is required for this purpose. In general, MRI is preferred over CT owing to its superior tissue contrast resolution and sensitivity to detect both the tumor and post-treatment changes. Using contrast enhanced techniques, the absence of uptake within the tumor is considered to

reflect necrosis while persisting uptake indicates vital tumourous tissue. Rim contrast enhancement after ablative loco-regional therapy is not indicative of a viable tumor unless contrast enhancement also reveals nodular or thick uptake along the tumor margins or a clear wash-out (Chung 2012, Riaz 2009) [36,37]. Tum or recurrence is signaled by the re-appearance of vascular enhancement.

Stage-adapted therapy for liver cancer

The two key factors that are most important in determining a patient's prognosis and potential treatment options are the tumor mass and hepatic functional reserve. Patients with early HCC have excellent chances for curative cancer treatment. They can achieve 5-year survival rates of 50-70% by surgical resection, liver transplantation, or percutaneous ablative procedures. With more advanced HCC, local transarterial embolization and multikinase inhibitor therapy can still prolong life. Figure 2 gives a summary and concise overview of stage-adapted therapy for hepatocellular carcinoma. Potentially curative therapy in BCLC stages 0-ASurgical resection constitutes the backbone of curative treatment in patients with early HCC. It is the treatment of choice in patients with localized tumor spread and small-sized cancers and tumors in a non-cirrhotic liver decided to decrease the chance of postoperative liver failure. sufferers must have best reasonably impaired liver function (child's level A cirrhosis), and have to no longer have portal high blood pressure (hepatic-portal vein strain gradient>10 mm Hg, presence of oesophageal varices or splenomegaly together with reduced platelet counts <100,000/µl) and needs to have serum bilirubin in the normal range. sufferers with tumor invasion of a first-rate portal or Hepatic vein, direct invasion of neighboring organs apart from the gallbladder, peritoneal disease and nodal or distant secondaries are not applicants for surgical treatment. potentially curative partial hepatectomy is the most effective treatment for HCC in sufferers with good enough hepatic purposeful reserve. Right hemi hepatectomy in cirrhotic patients has a higher chance of inducing hepatic decompensation than left hemi-hepatectomy. Non-anatomic resection can be vital to decrease the lack of useful liver parenchyma. Operative mortality for HCC is associated with the severity of liver disease, and patients with complications of cirrhosis along with marked portal high blood pressure, ascites, or bleeding have an inadequate hepatic reserve to face up to resection. maximum deaths are due to postoperative liver failure and < 10% are associated with complications of bleeding. 90-day mortality fees appear an extra dependable indicator of consequences than 30-day peri operative mortality, especially in patients with extended resections and resections of cirrhotic livers, since revolutionary jaundice, ascites, and sooner or later demise broaden slowly and well after 30 days in sufferers with marginal residual liver characteristic. In words, common prognostic gear, e.g., the kid-Pugh classification or the model for end-level Liver disorder

(MELD) score, is now not good enough to identify patients with inadequate hepatic practical reserve after resection. quantity and characteristics of the residual liver remnant may be decided via hepatic volumetry that's high-quality achieved before and after portal vein embolization. additionally, CLIP and ALBI scores help to evaluate the hepatic practical reserve and hazard of surgical resection. because hepatic regeneration is impaired in cirrhosis, resection, in general, ought to no longer exceed 25% of the liver parenchyma. Preoperative portal vein Embolization maybe utilized in selected sufferers to boom the volume of the liver Remnant before essential liver resections, in particular for right-sided tumors because it initiates hypertrophy and lets in for more full-size resections (Abulkhir 2008, Leung 2014)[38,39].Selective arterial chemoembolisation (TACE) has been encouraged as a complementary system before the portal vein embolization because it reduces arterial blood supply to the tumor and also embolisms potential arterioportal shunts (Yoo 2011).

Liver transplantation is an alternative therapeutic option if the liver cancer cannot be cured by local resection due to anatomical reasons, if residual liver function after resection is anticipated to be poor, or if there is a multi-nodular tumor spread into both liver lobes (grade IIIA evidence). Virtually all patients considered for liver transplantation are unresectable due to the degree of liver dysfunction rather than tumor

extent. Commonly, patients with HCC are selected for liver transplantation according to the so-called Milan criteria, i.e., the patient has a single nodule of less than 5 cm in diameter or at most 3 nodules, none of which exceeds 3 cm in diameter (Mazzaferro 1996). Patients who meet the Milan criteria usually achieve survival rates of 80% and 70% one and five years after liver transplantation. However, it has been demonstrated that selected patients with more extensive stages of liver cancer can be transplanted with reasonable long-term outcomes (Yao 2001) [40]. Selection of patients according

to the San Francisco criteria comprises solitary large nodules up to 6.5 cm as well as multi-nodular HCC with a maximum of 3 nodules, each of which must be smaller than 4.5 cm with a total sum of all nodule diameters less than 8 cm. Patients who remain within these extended selection criteria can still reach 70-80% five-year survival rates after liver transplantation. However, there is very limited data to support extending the selection criteria for liver transplantation further (Pomfret 2010) [41]. A central issue in liver transplantation is the process of fair organ allocation. Shortage of donor organs is particularly critical in patients with liver cancer, because the tumor will continue to expand while the the patient is on the waiting list, and can ultimately reach a stage that makes liver transplantation is a futile option. It has been estimated that after one year on the waiting list, approximately 40% of patients can no longer be cured by liver transplantation (Poon2007) [42]. In the Euro transplant registry donor's livers are allocated to patients according to their MELD scores. To circumvent the problem that patients with early HCC who are eligible for liver transplantation has rather low MELD scores, Euro transplant accepts the diagnosis of HCC within the Milan criteria as so-called standard exemption, allocating additional points on top of the patient's lab MELD score in an incremental time-dependent fashion. EASL/EORTC guidelines recommend treating liver cancers locally when the expected time on the waiting list exceeds 6 months (EASL/EORTC 2012) [43]. Bridging therapy

Can be done by transarterial chemoembolisation, radiofrequency ablation, or partialresection. This strategy probably also facilitates patient selection for liver transplantation, because those with stable disease after chemo embolization achieve a greater than 90% five-year survival rate after liver transplantation, while only 35% of patients, in the group with progressive tumor expansion survive five years post liver transplantation (Otto 2006).[44] Sirolimus, an inhibitor of mammalian target of rapamycin (mTOR inhibitor) seems to be a promising immunosuppressive agent in liver transplantation of HCC, because it has anti-proliferative activity against HCC in vitro and in vivo can interfere with vascular endothelial growth factor (VEGF). Several early reports suggested a lower risk of post-transplant HCC recurrence with the use of Sirolimus, and a registry-based comparison of 2491 adult patients with liver cancer, who underwent transplantation, versus 12,167 liver transplantation for other diagnoses suggested a post-transplant survival benefit of the use of Sirolimus, which was specific to patients transplanted for HCC (Toso 2010) [45]. In support, a recent meta-analysis suggested that sirolimus-based regimens significantly decreased overall tumor recurrence rates and recurrence-associated mortality (Menon 2013)[46] .Although these data are encouraging, the International Consensus Conferences on Liver Transplantation for HCC do not yet generally recommend Sirolimus for transplantation in HCC, since available data are entirely derived from retrospective studies (Clavien 2012).[47] Everolimus, a semi synthetic form of Sirolimus may have similar effects as Sirolimus but has not been studied adequately in patients with HCC. Side effects of Sirolimus comprise thrombosis of the hepatic artery, delayed wound healing, incisional hernias, hyperlipidemia, bone marrow suppression, mouth ulcers, skin rashes, albuminuria, and pneumonitis. Because of their side effect profile, in particular, hepatic artery thrombosis, mTor inhibitors should not be used in the first three months after liver transplantation. Non-surgical local procedures: Image-guided ablation is recommended for patients with early HCC when surgical options are precluded. Radiofrequency ablation (RFA) is currently considered the standard technique because most clinical data are available for RFA: A cohort study on percutaneous radiofrequency ablation demonstrated that complete ablation of lesions smaller than 2 cm is possible in more than 90% of patients with local recurrence in less than 1% (Livraghi 2008) [48]. In larger tumors, five-year survival rates are somewhat lower, at 70-80% for nodules less than 3 cm in diameter, and 50% for tumors between 3 and 5 cm (Lopez 2006) [49]. A cumulative meta-analysis has suggested that survival is better after radiofrequency ablation than after ethanol injection (Cho 2009). In up to a third of patients a self-limited post-ablation syndrome has been reported after RFA which was associated with fever, malaise, chills, right upper quadrant pain, nausea, and elevated liver enzymes (Dodd 2005) [50]. RFA is avoided for lesions in the hepatic dome or along the inferior liver edge to avoid diaphragmatic injury or intestinal perforation. In addition to size, the local efficacy is also affected by the proximity of a lesion to large

blood vessels (Lu 2005) [51], probably because the blood flow carries away heat from the lesions (the "heat sink" phenomenon). Following RFA gas bubbles may form in the liver as a result of treatment and should not be mistaken for infection or infarction (Park 2008) [52]. Although RFA is relatively well tolerated, severe and potentially fatal complications can occur, e.g., liver abscess, pleural effusion, pneumothorax and skin burns, sub capsular hepatic hematoma, and needle tract seeding of tumor cells (Takaki, 2013) [53]. Outcomes of RFA are superior to percutaneous ethanol injection and may

be equivalent to surgery in small tumors. Some alternative treatment modalities have recently attracted attention because they may overcome some of the limitations associated with RFA. Microwave ablation (MWA) can generate very high temperatures in the tumor tissue in a very short time. This can potentially lead to enhanced treatment efficacy and larger ablation zones and can reduce susceptibility to heat dispersion by blood flow in major vessels (Boutros 2010) [54]. Cryoablation refers to methods, which destroy tissue by local freezing or alternating freezing and thawing. Rapid tissue freezing and thawing produce a cytotoxic effect by disrupting cellular membranes and inducing cell death. The cryo lesion is hypoechogenic and can be visualized and monitored by intraoperative ultrasound. Cryoablation can lead to equivalent treatment outcomes as RFA (Wang 2015) [55]. However, meanwhile, most centers have abandoned cryoablation, because other techniques, e.g. RFA is technically easier to do, and may potentially be associated with less local recurrence and lower complication rates.Irreversible electroporation

(IRE) induces cell death by repeated application of short-duration high-voltage electrical pulses, which irreversibly injure cellular membranes. Although hyperthermic effects may occur with high-power applications, cell death associated with IRE is induced non-thermally. Hence, cooling owing to high perfusion is not a problem with this technique (Scheffer 2014). However, general anesthesia with neuro muscular blockade and cardiac gating to prevent arrhythmias are required. Other energy-based ablation treatment approaches comprise laser-induced thermal therapy (LITT) and high-intensity focused ultrasound (HIFU). Efficacy and safety of HIFU for primary or recurrent HCC has been predominantly studied in Hong Kong and appeared similar to outcomes with RFA. However, clinical experience outside of China is rather limited, since only a few centers worldwide have adopted these techniques. Thus, the place of HIFU is currently undefined. Adjuvant therapy, in the context of resection, liver transplantation, or local-ablative procedures do seem to offer additional benefits. Thus far, antiviral treatment of hepatitis B with nucleos(t)ide analogs remains the single approved treatment after removal or local destruction of HCC. Interestingly, one study (Su2014) reported that recurrence-free survival and overall survival was significantly better in 9,461 Taiwanese patients who had liver resections for HBV-associated HCC between 1997 and 2011, when they were on anti-platelet therapy. A randomized phase 3 trial involving 1,114 HCC patients after liver resection or local ablation, who were randomized to receive either sorafenib or placebo for 4 years or until tumor recurrence (STORM trial), did not meet its primary and secondary endpoints of recurrence-free survival, time to recurrence or overall survival [Bruix 2015]. Positive reports are available from phase 2 trials with transarterial radioactive 131-iodine, capecitabine, heparanase and thalidomide. However, confirmatory phase 3 data are not yet available for any of these agents. Tumor recurrence is frequent after putatively curative treatment of HCC. Although there is no generally accepted consensus on post treatment surveillance, most centers apply CT or MRI imaging every 3 to 6 months for the first two years after therapy, then annually, and if initially elevated, also recommend monitoring serum AFP every 3 months for the first two years, then every 6 months [Clavien 2012]. Most HCC recurrences are intrahepatic and reflect local recurrence or a new second primary lesion [Hatzaras 2014]. The best predictors of HCC recurrence are high serum alpha-fetoprotein levels (AFP >500 ng/mL), microvascular invasion and/or additional tumor sites besides the primary lesion. Solitary nodules might be amenable to repeat resection, but HCC recurrence is frequently multifocal owing to intrahepatic dissemination of the tumor. Some patients with HCC recurrence after primary resection might benefit from salvage transplantation. The role of HBV infection for HCC recurrence after resection is under debate [Sun 2007, Cescon 2009, Char 2014], and early HCC recurrence has been reported to be even greater in hepatitis C-infected patients than HBV-infected patients.

[Utsunomiya 2015]. Therapy with antiviral drugs seems to reduce late (≥ 2 years) HCC recurrence in chronic hepatitis B and C does not seem to have much effect on early HCC recurrences [Yin 2013, Huang 2015]. The effects of direct antiviral therapy in patients with HCV-related HCC are not yet clear, since rapid recurrence and expansion of HCCs have been reported to occur shortly after DAA therapy, even when the primary HCC had been “cured” quite some time before [Conti 2016, Kozbial 2016, Reig 2016]. and overall survival was significantly better in 9,461 Taiwanese patients who had liver resections for HBV-associated HCC between 1997 and 2011 when they were on antiplatelet therapy. A randomized phase 3 trial involving 1,114 HCC patients after liver resection or local ablation, who were randomized to receive either sorafenib or placebo for 4 years or until tumor recurrence (STORM trial), did not meet its primary and secondary endpoints of recurrence-free survival, time to recurrence or overall survival [Bruix 2015]. Positive reports are available from phase 2 trials with transarterial radioactive 131-iodine, capecitabine, heparanase and thalidomide. However, confirmatory phase 3 data are not yet available for any of these agents. Tumor recurrence is frequent after putatively curative treatment of HCC. Although there is no generally accepted consensus on post treatment surveillance, most centers apply CT or MRI imaging every 3 to 6 months for the first two years after therapy, then annually, and if initially elevated, also recommend monitoring serum AFP every 3 months for the first two years, then every 6 months [Clavien 2012]. Most HCC recurrences are intrahepatic and reflect local recurrence or a new second primary lesion [Hatzaras 2014]. The best predictors of HCC recurrence are high serum alpha-fetoprotein levels (AFP >500 ng/mL), microvascular invasion and/or additional tumor sites besides the primary lesion. Solitary nodules might be amenable to repeat resection, but HCC recurrence is frequently multifocal owing to intrahepatic dissemination of the tumor. Some patients with HCC recurrence after primary resection might benefit from salvage transplantation. The role of HBV infection for HCC recurrence after resection is under debate [Sun 2007, Cescon 2009, Char 2014], and early HCC recurrence has been reported to be even greater in hepatitis C-infected patients than HBV-infected patients

[Utsunomiya 2015]. Therapy with antiviral drugs seems to reduce late (≥ 2 years) HCC recurrence in chronic hepatitis B and C does not seem to have much effect on early HCC recurrences [Yin 2013, Huang 2015]. The effects of direct antiviral therapy in patients with HCV-related HCC are not yet clear, since rapid recurrence and expansion of HCCs have been reported to occur shortly after DAA therapy, even when the primary HCC had been “cured” quite some time before [Conti 2016, Kozbial 2016, Reig 2016]. non-surgical HCC who are also not suited for percutaneous ablation and do not have extra hepatic tumor spread. HCC exhibits intense neoangiogenic activity so that even well-differentiated HCCs become highly dependent on arterial blood supply. Thus, hepatic arterial obstruction is performed either by angiographic transarterial embolization or transarterial chemoembolisation. Usually, lipiodol combined with an embolism agent such as gelatin or microspheres is mixed with cytostatic drugs and applied to the liver via an intra-articular catheter. Suitable cytotoxic agents are doxorubicin, mitomycin, and cis-platinum, but the optimal combination of drugs and treatment schedules has not been established. In randomized studies demonstrating the benefit of chemoembolization, doxorubicin or cis-platinum was administered in 3-4 angiographic sessions per year. Chemoembolization carries the risk of ischemic damage to the liver, potentially leading to fulminant liver failure. To minimize this risk chemoembolization should be offered only to patients with good residual hepatic function, who have asymptomatic multi-nodular liver cancer without vascular invasion or extra hepatic tumor spread. Vice versa patients with decompensated liver disease (liver cirrhosis, Child’s B or C) or imminent hepatic failure should not undergo chemoembolization. Table 2 lists absolute and relative contraindications for chemoembolization. The side effects of intra-articular chemoembolization are the same as for systemic chemotherapy and consist of nausea, vomiting, bone marrow depression, alopecia, and renal damage. TACE is a risk factor for hepatitis. B virus reactivation and antiviral prophylaxis are recommended in HBsAg-positive patients. Common ischemic complications comprise a hepatic abscess, acute cholecystitis, and damage to biliary tracts. Interstitial pneumonitis and gastrointestinal ulcerations due to abnormal shunting

may occur owing to radiation injury. Pulmonary or cerebral lipiodol embolization are rare but potentially fatal complications. Overall, treatment-related mortality rates are about 2%. As a frequent complication of hepatic ischemia, more than 50% of patients also develop a so-called post-embolization syndrome with fever, abdominal pain, and a moderate degree of ileus. Fasting and fluid replacement is mandatory, but the post-embolization syndrome is usually self-limited and patients can be discharged safely after 2 days. Objective response rates vary between 16% and 60%, but less than 2% of patients achieve complete remission. Residual tumor cells recover their blood supply and the tumors continue to grow. Thus, repeated therapy may be needed. However, multiple courses can increase death from liver failure despite good tumor

reduction; thus, counterbalancing the potential survival benefits from repeated treatment. TACE should be limited to the minimum number of interventions needed to control tumor growth. Chemoembolization is currently considered to significantly improve survival in suitable palliative patients [Llovet 2002]. Beyond that, combination therapy with TACE and RFA appears to be the most efficient treatment of early HCC [Lan 2016] and is used as bridging therapy for HCC patients on the waiting list for liver transplantation. However, its use in patients allocated to curative resection it is not recommended because surgical complication rates are increased thereafter. Randomized controlled trials evaluating radio embolization to different remedy strategies are not available. but there is amassing suitable proof from numerous properly characterized massive cohort studies [Hilgard 2010, Salem 2010, Sangro 2011, Mazzaferro 2013]. Taking into account tumor level, intermediate tumor level sufferers dealt with via radio embolization reap sixteen to 18 months of median survival time [Salem 2010, Sangro 2011, Mazzaferro 2013]. detrimental activities, reaction fees, and time to development appeared to enhance at the same time as normal survival become equal whilst radio embolization became in comparison to chemoembolization [Salem 2011]. while down-staging to transplantation is allowed using local policies, radio embolization outperforms chemoembolization [Lewandowski 2009]. ultimately, a randomized managed phase 3 trial in 467 sufferers evaluating radio embolization to sorafenib chemotherapy no longer monitors any enormous survival distinction among the two treatment palms (SIRT: 8.0 months as opposed to sorafenib nine. nine months; p=zero.18) [Villain 2017]. Systemic chemotherapy with conventional anti-cancer pills does now not seem to provide survival blessings, whether given as an unmarried agent or as part of aggregate chemotherapy [Llovet 2003]. Likewise, anti-hormonal remedy with tamoxifen or octreotide has not furnished progressed affected person survival whilst studied under controlled situations [Gallo 2006, Yuen 2002]

Systemic palliative HCC therapies

Molecular-targeted therapeutic strategies offer new hope for effective palliative therapy in liver cancer. Sorafenib (Nexavar®) is an orally available multi-kinase inhibitor acting on several distinct tyrosine kinases (VEGFR2, PDGFR, c-kit receptor) as well as on serine/threonine kinases (b-Raf and p38). Thus, by inhibiting angiogenesis and cellular proliferation, sorafenib can block two of the majors signaling pathways of HCC expansion. In a phase 3 study (the SHARP trial) involving 602 patients, sorafenib 400 mg BID was moderately well-tolerated and associated with improved survival in 44% of patients resulting in 3 months extended survival in treated patients (10.7 months in the sorafenib arm versus 7.9 months in the control arm). The efficacy of sorafenib has been confirmed in a second randomized placebo-controlled trial, mostly involving patients with HBV-associated HCC [Cheng 2009] and in 1586 patients of the GIDEON

(Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of its Treatment with Sorafenib) prospective database (Lencioni 2012). Sorafenib has established itself as the first option for patients with HCC can no longer be treated with local therapies. The SHARP trial largely included patients with preserved liver function. Although the pharmacologic profile is favorable, data on Child-Pugh class B patients are scarce [Abou Alfa 2011]. Patients with liver cirrhosis Child class C, however, do not achieve a survival benefit from sorafenib and should only receive the best supportive care. Diarrhea, weight loss, hand-foot syndrome, and rash, hypertension, renal toxicity with hypophosphatemia, thromboembolism, bleeding, cardiotoxicity, thyroid dysfunction, pruritus, alopecia, impaired wound healing and hepatotoxicity are important side effects of sorafenib. Sorafenib has also been associated with fulminant hepatic toxicity, which is characterized by elevated aminotransferases, coagulopathy, and hyperbilirubinemia. Sorafenib is particularly effective in HCC related to chronic hepatitis C. However, its role in the treatment of recurrent HCC after liver transplantation currently remains still undefined. Sorafenib can be safely combined with chemoembolization therapy [Pawlik 2011] but this combination does not provide any clinical benefit. Likewise, in the SORAMIC study, the combination of sorafenib with 90 Yttrium radiotherapy (SIRT) did not result in better survival than sorafenib alone. However, certain patient subgroups, e.g., young patients, non-cirrhotic patients or those with a non-alcoholic etiology may still benefit from a SIRT/sorafenib combination treatment. Lenvatinib (Lenvima®), is an inhibitor of VEGF receptors 1-3, FGF receptors 1-4, PDGF receptor a, RET, and KIT show activity in hepatocellular carcinoma. The phase III REFLECT study comparing lenvatinib (8-12mg/d) to sorafenib (400 mg twice daily) in untreated patients with advanced hepatocellular carcinoma revealed that lenvatinib was not inferior to sorafenib and improved survival to 13.6 (12.1-14.9) months (sorafenib 12.3 (10.4-13.99 months n.s.) [Kudo 2017]. Quality of life scores deteriorated in both treatment groups after treatment with rather similar toxicity profiles: However, patients, who received lenvatinib, experienced fewer instances of palmar-plantar erythrodysesthesia, diarrhea, and alopecia but more instances of arterial hypertension, proteinuria, dysphonia, and hypothyroidism. In summary, lenvatinib has been approved in Japan, Europe, and the US as a second, first-line treatment option in patients with advanced hepatocellular carcinoma. The safety of lenvatinib and its use in combination regimens is further evaluated in multiple ongoing studies. Other antagonists targeting VEGFR, EGFR, ERBB2, Akt-mTor, or Wnt/β-catenin signal transmission pathways have been evaluated in HCC. However, sunitinib, brivanib, linifanib, tivantinib, or the combination of erlotinib with sorafenib, everolimus, and ramucirumab, all have failed to demonstrate relevant survival benefits.

Regorafenib (Stivarga®) is a small molecule multikinase inhibitor with a structural analogy to sorafenib. Regorafenib targets VEGF receptors 1-3, TIE2, PDGFRß, FGFR, RET, KIT, RAF kinase, and MAPK thus intensively inhibits several pathways involved in angiogenesis, oncogenesis, metastasis, and tumor immunity. In the RESOURCE phase 3 trial regorafenib met its primary study endpoints and revealed prolonged survival (10.6 versus 7.8 months) and better disease control than placebo in patients who had failed on sorafenib [Bruix 2016]. Thus, regorafenib has recently been licensed

for HCC patients progressing on first-line drug treatment. The most common adverse effects of regorafinib were rash and hand-foot syndrome, hypertension, increased AST, and hyperbilirubinemia. Similar to sorafenib skin toxicity with regorafenib was associated with improved overall survival [Bruix 2018]. Of note, re-analysis of the data from the REFLECT study, where 75% of patients subsequently were treated with sorafenib, suggests that sorafenib may offer an alternative second-line treatment strategy for patients with HCC who had received lenvatinib as a first-line drug. The multikinase inhibitor cabozantinib (Cabometyx®) is active against VEGFR2, c-MET, AXL, RET, Kit, and FLT3. Beyond angiogenesis and oncogenesis inhibited kinases are implicated also in pathways of resistance to VEGFR inhibitors such as sorafenib. Consequentially cabozantinib was tested as a second-line treatment versus placebo in 707 patients with advanced HCC who received up to 2 prior system treatment regimens (including sorafenib) and who had disease progression (CELESTIAL trial) (Abou-Alfa GKI 2018). In this study Cabozantinib substantially improved overall survival versus placebo (median 10.2 versus 8 months) and the benefit was more pronounced when patients received sorafenib because of the simplest earlier therapy (11. three versus 7.2 months). Cabozantinib additionally achieved extra development-loose survival (5.2 versus 1.9 months) and for this reason, has emerged as licensed as a 2d-line treatment option for sufferers failing on or intolerant to sorafenib. Dose reductions have been common inside the remedy arm (sixty-three%), frequently due to aspect results (16%) inclusive of hand-foot pores and skin response, hypertension, multiplied liver enzymes, fatigue, diarrhea, asthenia, and decreased urge for food. for this reason, the terrible tolerability of

cabozantinib may also limit its use in medical practice. Ramucirumab (Cyramca®) is a humanized monoclonal antibody that selectively inhibits VEGFR2 and confirmed interest in HCC in early trials. Of observation, the attain trial of ramucirumab in opposition to a placebo indicated a survival gain, particularly for the subgroup of HCC patients with elevated AFP tiers [Zhu 2015]. This observation shaped the basis for the biomarker-pushed reach-2 trial, which evaluated ramucirumab versus placebo in advanced HCC sufferers with failure of or intolerance to sorafenib and excessive AFP (≥400 ng/ml) [Zhu 2019]. attain-2 met its number one study endpoint and confirmed that ramucirumab stepped forward general survival (8. five verses 7.3 months, p=0.02) and development-loose survival (2.8 as opposed to 1.5 months, p<zero.0001). A pooled safety and efficacy evaluation of the reach-2 trial with the patients who had AFP degrees ≥four hundred ng/ml within the attain have a look at showed those findings [Zhou 2018] so that ramucirumab has been certified as a biomarker-managed 2nd-line remedy for the subgroup of HCC patients with excessive AFP. Ramucirumab has a viable protection profile with hypertension and hyponatremia as the most commonplace facet consequences. On the other hand, it revealed declines in ailment-related symptoms, making it a 2d-line drug demonstrating both advanced survival and nice of existence. Immune-primarily based therapy. presently, most cancers immunotherapy has emerged as encouraging due to the fact monoclonal antibodies (mAbs), which block molecules that negatively adjust T-cell responses, can opposite T-cellular exhaustion and reconstitute anti-tumour immunity [Prieto 2015]. Immune checkpoint inhibitors, which include ipilimumab (anti-CTLA-4), nivolumab (anti-PDL1), and pembrolizumab (anti-PD-1) has already obtained approval from regulatory corporations for the therapy of cancer, lung, and renal cancers.Checkpoint inhibitors reactivate the exhausted antitumor response and might bring about a goal and maintained immune control of tumor growth. preliminary data from the CheckMate 040 examination, an open-label phase half of dose escalation and expansion trial with the intravenous bi-weekly application of the PD-L1 antagonist nivolumab, pronounced 20% goal response rates throughout all underlying etiologies of liver cancer [El-Khoueiry 2017]. however, the results of a randomized controlled segment 3 trial, CheckMate 459, did not reach its primary examine endpoint. The PD-1 inhibitor pembrolizumab triggered entire remission, in 1% and partial remission in sixteen.3% of 104 sufferers with advanced liver most cancers, who had disease progression on sorafenib in the KEYNOTE-224 phase 2 study but likewise failed to reach its primary study endpoint in the KEYNOTE-240 trial. Based on their phase II data both nivolumab (Opdivo®) and pembrolizumab (Keytruda®) were licensed for patients with advanced HCC in the US but not in Europe. However, both antibodies are further evaluated as components in various combination rescue studies for patients with progressive HCC. The spectrum of adverse effects associated with nivolumab and pembrolizumab comprises a variety of autoimmune and graft-versus-host-disease like reactions such as skin disease, diarrhea, thyroiditis, and autoimmune-like hepatitis but overall side effects appear still to be acceptable. Recently, a phase III a study comparing the combination of monoclonal antibodies atezolizumab and bevacizumab versus sorafenib (IMbrave150 study; Cheng AL et al. ESMO Asia 2019) has created new hope, because the combination resulted in substantially improved survival, delay of disease progression, and quality of life across almost all groups of patients at acceptable adverse effects. However, patients with liver cancer of non-viral etiology appeared to have less benefit from this novel systemic treatment option.

Prophylaxis of liver cancer

Despite conspicuous progress in the diagnosis and therapy of HCC, the prognosis of HCC has not improved very much over time. Thus, prophylactic measures are of pivotal importance. HBV vaccination, now recommended

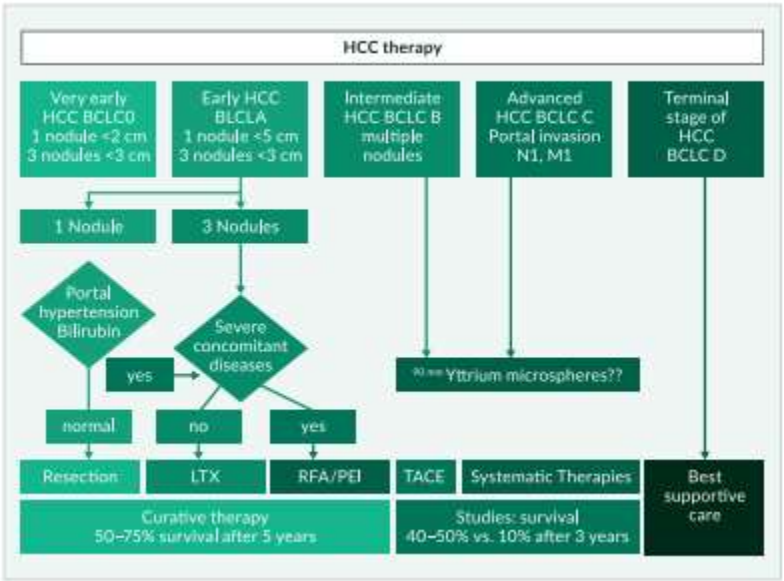

Table : Overview of stage-adapted therapy of liver cancer relative to the BLCL criteria.

*Systemic therapy comprises Sorafenib and Lenvatinib as first line options, Regorafinib, Cabozantinib, and Ramucirumab as further options after failure or intolerance of first line drug therapies.by many national vaccination councils, has been proven in Taiwan to markedly reduce HBV infection rates along with the incidence of HCC as a complication of chronic hepatitis B in later life [Lok 2004]. Patients with chronic HBV and patients with chronic hepatitis C should be offered antiviral therapy as effective secondary prophylaxis of HCC. Although HBe antigen positive [van Zonneveld 2004] and HBe antigen negative patients with chronic hepatitis B showed reduced incidence rates of HCC when successfully treated with interferon [Papatheoridis 2001, Brunetto 2002, Lampertico 2003], antiviral therapy with nucleos(t)ide analogs seem to

reduce the risk of HCC less convincingly [Papatheoridis 2010, Papatheoridis 2011]. Newer, more potent nucleos(t)ide analogs such as entecavir seems to reduce the risk of HBV-associated liver cancer more potently, particularly in high-risk patient groups [Hosaka 2012]. Systematic analysis of the available data suggests that HBV treatment can reduce the relative HCC risk by about 60%. Also, several meta-analyses suggest that successful interferon therapy will reduce the risk of HCC in chronic hepatitis C [Camma 2001, Paptheoridis 2001a, Veldt 2004]. Despite some initial confusion on the role of the newly available directly acting antiviral drugs in hepatitis C concerning HCC prevention it has meanwhile become clear that rates of HCC development are substantially diminished after DAA therapy [Carrat 2019]. Nevertheless, patients who have cirrhosis and/or long disease duration before antiviral therapy should be followed in HCC surveillance programs, since their risk of liver cancer remains still high even after achieving a sustained virological response [Yu 2006, Van der Meer 2012, Aleman 2013]. Improving additional risk factors such as obesity and poorly controlled diabetes mellitus may further reduce the risk of HCC development: weight reduction and exercise improve the prognosis of steatohepatitis, and metformin and thiazolidinedione should be favored over sulfonylurea drugs in the treatment of diabetes [Greten 2013]. The use of aspirin but no other nonsteroidal anti-inflammatory drugs were associated with a decreased risk of HCC in a US Diet and Health Study [Sahasrabuddhe 2012], and several studies suggest that the use of statins leads to a lower risk of HCC [Singh 2013, Shi 2014, Hsiang 2015]. Finally, daily consumption of two or more cups of coffee reduces the risk of HCC by 40-50% in patients with chronic viral hepatitis [Gelatti 2005, Bravi 2007, Larsson 2007, Wakai 2007].

Conclusions

Hepatocellular carcinoma is a competitive tumor related to bad analysis. Given it sasymptomatic nature in the early degrees, HCC is on the whole identified at advanced degrees, regularly main to incurable clinical situations. current and previous remedy options had been simplest modestly associated with expanded survival. In truth, the survival advantage with sorafenib was best for a few months. Now a days, newly rising healing goals, in addition to new pills and therapeutic modalities have been investigated in pre-medical and medical trials. until the discovery of curative therapy, or at least drug development with good-sized survival benefit, clinicians have to be cautious to screen for HCC in cirrhotic sufferers and prognosis must be finished at early tiers, so that if the HCC is identified soon sufficient for a liver transplant, the outcomes will be quite accurate. Ongoing Research should be carried out on all ability HCC targets, inclusive of the immunological, molecular, and translational tiers so that it will lessen the increasing HCC mortality

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Conflict of Interest

The authors declare no conflict of interest

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