World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i8.1193

World J Gastroenterol 2013 February 28; 19(8): 1193-1199
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

MINIREVIEWS

Management of small hepatocellular carcinoma in cirrhosis: Focus on portal hypertension

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Received: December 10, 2012 Revised: January 17, 2013
Accepted: February 5, 2013
Published online: February 28, 2013

Abstract

The incidence of hepatocellular carcinoma (HCC) is rising worldwide being currently the fifth most common cancer and third cause of cancer-related mortality. Early detection of HCC through surveillance programs have enabled the identification of small nodules with higher frequency, and nowadays account for 10%-15% of patients diagnosed in the West and almost 30% in Japan. Patients with small HCC can be candidates for potential curative treatments: liver transplantation, surgical resection and percutaneous ablation, depending on the presence of portal hypertension and co-morbidities. This review will analyze recent advancements in the clinical management of these individuals, focusing on issues related to the role of portal hypertension, the debate between resection and ablative therapies and the future impact of molecular technologies.

Key words: Portal hypertension; Hepatic venous pressure gradient; Clinically significant portal hypertension; Liver stiffness; Liver cancer; Hepatocellular carcinoma; Resection; Radiofrequency ablation; Percutaneous ethanol injection

Hernandez-Gea V, Turon F, Berzigotti A, Villanueva A. Management of small hepatocellular carcinoma in cirrhosis: Focus on portal hypertension. *World J Gastroenterol* 2013; 19(8): 1193-1199 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i8/1193.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i8.1193

INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) is rising worldwide being currently the fifth most common cancer and third cause of cancer-related mortality[1]. HCC accounts for more than 90% of primary liver cancers, and it usually arises in the setting of long-term underlying liver disease. In fact, HCC is now the first cause of death among cirrhotic patients[2]. According to the Barcelona Clinic Liver Cancer (BCLC) algorithm, HCC can be classified into 5 stages when considering variables related to tumor burden, liver function and health status. Additionally, this algorithm links tumor stage with a specific treatment strategy[3]. Despite recent advancements in HCC management such as the introduction of the molecular targeted agent sorafenib for advanced stages[4], the mainstream potential curative therapies in HCC are still resection, transplantation and percutaneous ablation.

HCC surveillance programs for cirrhotic patients have enabled the identification of small nodules with higher frequency[5], and nowadays account for 10%-15% of patients diagnosed in the West and almost 30% in Japan[6]. "Small HCC" is a term frequently used to define tumors less than 2 cm in diameter. This cut-off is based

on the outstanding outcomes of patients with these tumors treated with surgical resection when compared to those with larger ones[7]. However, small HCC can be two different entities in pathology: vaguely and distinctly nodular[7]. Vaguely nodular tumors are well-differentiated without local invasiveness and around 12 mm in size; whereas distinctly nodular are frequently larger (16 mm) and often show local invasiveness features such as microvascular invasion[8]. European Association for the Study of the Liver (EASL) and American Association for the Society of Liver Diseases (AASLD) guideless for HCC management enables an accurate diagnosis of tumors larger than 1 cm in cirrhotic livers when a dynamic imaging technique [computed tomographic (CT) or magnetic resonance (MR)] show the so-called "hallmark" features of HCC: uptake in the arterial phase with early wash-out in the portal phase[9]. For nodules between 1-2 cm, this criterion is still maintained particularly in referral centers with a dense experience in HCC management. In case these imaging features are absent, diagnosis still requires a biopsy. According to the BCLC algorithm, patients with small HCC can be candidates for potential curative treatments, depending on portal hypertension and co-morbidities. This short review will analyze recent advancements in the clinical management of these individuals, focusing on issues related to the role of portal hypertension, the debate between resection and ablative therapies and the future impact of molecular technologies.

TREATMENT STRATEGY OF SMALL HCC AND IMPACT OF PORTAL HYPERTENSION ON POSTOPERATIVE OUTCOME

The EASL[9] and AASLD[10] guidelines recommend three alternatives for the treatment of patients with small HCC, depending on the presence of portal hypertension and co-morbidities: liver transplantation, surgical resection and percutaneous ablation. Overall, these therapies achieve a 5-year survival rate between 60%-75% in early HCC (BCLC 0/A), even though in small HCC survival rates can even be higher. About 80% of HCC develop in patients with underlying chronic liver disease, where liver failure and portal hypertension may be present. Since different treatment options are available for patients with small HCC, allocation to a given option should rely on evidence-based criteria, considering expected outcomes rather than merely treatment feasibility[11].

As for surgical resection, peri-operative mortality has decreased to 2%-3% with current surgical techniques. On the other hand a pioneer study by our group in Barcelona[12] showed that in a series of 29 Child A cirrhotic patients and HCC less than 5 cm undergoing liver resection surgery, hepatic venous pressure gradient (HVPG) $\geqslant$ 10 mmHg was independently associated with unresolved decompensation 3 mo following surgery. In a larger series published later, post-operative survival of patients with Child A cirrhosis without clinically significant portal hypertension (CSPH) was 70% at 5 years, while it dropped to 25%-50% in patients with CSPH[3]. In addition, even small increases in bilirubin, above the 1 mg/dL cutoff, were also independently associated with increased mortality. The impact of PH-related variables on the risk of post-operative liver failure and mortality has been confirmed in many Western and in Eastern series[3,12-24] (Table 1). In these studies 3-year survival was in mean 59% (range: 45%-71%) in patients with clinical signs of portal hypertension, while it increased to 72% (62%-81%) in patients without any clinical sign of the syndrome. A similar difference is observed analyzing post-opertative liver decompensation and 5-year survival, and similar results were obtained in a Japanese cohort of resected HCC[25]. Overall these data show that even if the presence of CSPH is not an absolute contraindication for performing liver resection for HCC, it clearly increases the risk of post-operative complications and death, suggesting that other available options such as liver transplantation (see below) should be considered in this subgroup of patients. Hence, the best candidates for surgical resection are patients with solitary tumors, preserved liver function and absence of CSPH. Consequently, the European and American Associations for the study of the Liver (EASL[9] and AASLD[10]) guidelines for HCC management recommend surgical resection as the first-line option in patients with small HCC without CSPH or liver dysfunction.

A main drawback of liver resection is the risk to develop a tumor recurrence, that accounts for 70% at 5 years[26] either because of true metastasis or *de novo* HCC.

By definition, patients with small HCC are within Milan criteria for liver transplantation[27], and besides treating the tumor liver transplantation provides a solution for the underlying liver disease. However, the scarcity of donors limits its feasibility and increases time in the waiting list. Even though there are no robust data, the risk of dropout from the waiting list seems lower in patients listed with small HCC. Hence, liver transplantation is the best option for patients in BCLC stage 0/A, CSPH and absence of other medical conditions that contraindicate this procedure.

Local ablation

Local ablation is considered as a competitive alternative to resection or transplantation in patients with small HCC[28] not suitable for surgery. Both radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI) are standard of care techniques for tumor ablation, being used worldwide. They are both able to induce necrosis through different mechanisms. PEI presents a higher post-treatment rate of recurrence that can reach 40% at two years in larger lesions[29,30]. RFA has shown its ability to better control the disease with a lower local recurrence rate (2%-18% at 2 years) when compared with PEI (11%-45%) in randomized control trials (RCT)[31-35]. However, differences in survival were not described. Therefore, current guidelines recommend the use of PEI in cases where RFA is not feasible for technical reasons[9]. Five-year

Table 1 Relevant reported studies describing the impact of hepatic venous pressure gradient or portal-hypertension related variables in patients with potentially resectable or resected hepatocellular carcinoma

Ref.	Patients included (*n*)	Portal hypertension-related variables studied	Outcome
Llovet *et al*[3]	43	HVPG	CSPH independently associated with 5-yr post-operative mortality
Bruix *et al*[12]	29	HVPG	CSPH independently associated with PLF at 3-mo
Berzigotti *et al*[13]	63	Spleen size; platelet count; platelet count/spleen diameter; liver stiffness; LSPS PH risk score	Best single predictor of CSPH: liver stiffness; combination with spleen size and platelet count improved the results (AUROC LSPS 0.852; PH risk score 0.884)
Boleslawski *et al*[14]	43	HVPG Platelet count; spleen size; esophageal varices = indirect signs of PH	CSPH independently associated with increased PLF and 90-d mortality. Indirect signs of PH showed no discriminative ability
Capussotti *et al*[15]	217	Platelet count; spleen size; esophageal varices	PH associated with lower 3-yr and 5-yr survival
Cescon *et al*[16]	90	Liver stiffness; platelet count; spleen size; esophageal varices	LS (but not other signs) independently associated with the risk of PLF
Chen *et al*[17]	190	Intraoperative measurement of PVP	PVP independently associated with PLF on multivariate analysis
Cucchetti *et al*[18]	241	Platelet count; spleen size; esophageal varices	PH associated with lower 3-yr and 5-yr survival, but not after adjusting for MELD, albumin and extent of resection no
Figueras *et al*[19]	39	HVPG	CSPH associated with increased risk of morbidity
Giuliante *et al*[20]	588	Platelet count; spleen size; esophageal varices	PH independently associated with increased mortality
Imamura *et al*[21]	532	Varices, hypersplenism or hepatofugal portal flow	PH associated with a higher risk of post-operative ascites
Ishizawa *et al*[22]	203	Platelet count	Platelet count < 100×10^3/mL independently associated with PLF
Kim *et al*[23]	72	Liver stiffness	LS predicted PLF with good accuracy; LS better than ICG15
Llop *et al*[24]	79	Liver stiffness	CSPH predicted with good accuracy
Ishizawa *et al*[25]	434	Platelet count; spleen size; esophageal varices	PH associated with lower 3-yr and 5-yr survival

HVPG: Hepatic venous pressure gradient; PH: Portal hypertension; LS: Liver stiffness; PVP: Portal vein pressure; PLF: Post-operative liver failure; CSPH: Clinically significant PH (HVPG ⩾ 10 mmHg); AUROC: Area under receiver operating characteristic curve; MELD: Model for end-stage liver disease.

survival with RFA reaches 70%[36,37], with the best results in patients with good liver function (Child-Pugh A) and small tumors[38]. Although resection remains the first-line option for patients without CSPH, well-preserved liver function and solitary tumors less than 2 cm, there is an increasing debate as to whether ablative therapies (particularly RFA) could be a competitive option in these patients. Theoretically, in these solitary small tumors RFA could be as effective as surgery in terms of oncological results, and avoid all the possible complications related to the surgical procedure. However, available evidence is still limited as the few RCT available evaluating face-to-face both therapeutic options show controversial results (Table 2). In addition, there are several methodological issues that preclude reaching any robust conclusion from these trials (*e.g.*, treatment allocation, patient selection criteria, trial implementation, short follow-up, *etc.*). In fact, none of them was specifically design to only include patients with HCC less than 2 cm. Replacement of resection by RFA as first line therapy in patients with early HCC cannot be recommended at this point. Further evidence will be needed to appropriately address this issue.

Tumor recurrence is the main drawback in patients treated with resection or ablation, since the risk factor for HCC development (*i.e.*, cirrhosis) is still present[39]. Early recurrence usually occurs within the 2 years after surgery and it is due to true metastatic spread. However, late recurrence appears later on, usually beyond 2 years, and it is consider as *de novo* tumor developed as a consequence of the carcinogenic effect of underlying cirrhosis (field effect)[21]. Besides clinical differences[21], these two patterns of recurrence also differ in their molecular profile[40]. A large Japanese study found that non-anatomical resection, high AFP serum levels and presence of microscopic vascular invasion were risk factors for early recurrence, whereas grade of hepatitis activity, multiplicity and gross tumor classification impacted mostly late recurrence[21].

PORTAL HYPERTENSION ASSESSMENT IN PATIENTS WITH CIRRHOSIS AND SMALL HCC

The above-mentioned data underscore the need of an accurate discrimination of the presence of portal hypertension in patients with small HCC. Portal hypertension (PH) is a clinical syndrome hemodynamically defined as an increase in the pressure gradient across the liver (between portal pressure and inferior vena cava pressure) above the normal value of 5 mmHg[41]. In patients with cirrhosis, this gradient can be estimated by its clinical equivalent-the HVPG-which is assessed at hepatic vein catheterization and avoids the need to directly puncture the portal vein[41]. An elevated HVPG between 6 to 9 mmHg defines subclinical portal hypertension, whereas an HVPG ⩾ 10 mmHg defines clinically CSPH, since all the potential complications of the syndrome (*e.g.*, varices, ascites, *etc.*) can appear above this threshold[41]. The gold standard for the diagnosis and assessment of PH is the measurement of the HVPG, which is obtained as

Table 2 Randomized controlled trials comparing surgical resection and percutaneous ablation in patients with early hepatocellular carcinoma

Ref.	Treatment allocation	Sample size (*n*)	Serum bilirubin	Tumor median size	Nodules	Median follow-up	Recurrence rate	1/3/5 yr survival
Chen *et al*[17]	Multidisciplinary team of doctors	90 (resection)	> 2 mg/dL (33%)	< 3 cm (52%)	Single (100%)	NR	NR	94%/68%/NR
		71 (ablation)	> 2 mg/dL (26%)	< 3 cm (46%)	Single (100%)	NR	NR	93%/73%/NR
Huang *et al*[66]	Consecutive enrolment	38 (ablation)	NR	≤ 2 cm (55%)/2-3 cm (45%)	Single (79%)	37.7 ± 14.5	47%	100%/95%/92%
		38 (resection)	NR	≤ 2 cm (63%)/2-3 cm (37%)	Single (89%)	38.4 ± 16.4	39%	97%/89%/87%
Huang *et al*[67]	Consecutive enrolment	115 (ablation)	15.3 ± 4.6 μmol/L	≤ 3 cm (49%)	Single (73%)	NR	63%	86.9%/69.6%/54.78%
		115 (resection)	16.4 ± 5.3 μmol/L	≤ 3 cm (39%)	Single (84%)	NR	41%	98.26%/92.17%/75.6%
Feng *et al*[68]	Consecutive enrolment	84 (ablation)	17.2 μmol/L	≤ 2 cm (37%)/> 2 cm and < 4 cm (63%)	Single (57%)	NR	42%	96%/87.6%/NR
		84 (resection)	15.1 μmol/L	≤ 2 cm (30%)/> 2 cm and < 4 cm (46%)	Single (62%)	NR	32%	93.1%/83.1%/NR

NR: Not reported.

the difference between "wedged" (occluded) and "free" hepatic venous pressures. This method is safe, objective, reproducible, and accurate; and it provides prognostic information independent of liver function. It is currently the best marker to predict clinical events in patients with liver diseases within research protocols[42].

Since development of gastroesophageal varices is a direct consequence of CSPH, the presence of esophageal varices on endoscopy is a 100% specific sign of CSPH. However, approximately 50% of well compensated patients without any evident sign of portal hypertension (*e.g.*, without esophageal varices) already show CSPH on hemodynamic assessment[43]. In the specific setting of well-compensated patients without varices, CSPH independently increases the risk of developing esophageal varices, clinical decompensation and HCC during follow-up[43-45], resulting in a higher mortality. Hence, CSPH should be always assessed in patients with cirrhosis for prognostic stratification[41].

HVPG measurement has some limitations such as cost, invasiveness (even if minor) and the need for a specific training for its performance and interpretation. Since it is not available in all centers, noninvasive surrogate methods to diagnose portal hypertension are needed, and have been widely evaluated. Non-invasive markers include laboratory tests, ultrasonography and liver stiffness. Regarding routine laboratory tests, the objective components of Child-Pugh score (albumin, bilirubin, INR) correlate with HVPG[46-48] and with the prevalence and grade of esophageal varices in cirrhotic patients. Interestingly this correlation is also observed in patients with compensated cirrhosis[49] suggesting that there is a close correlation between liver structural damage and the onset of portal hypertension and hepatocellular dysfunction. Low platelet count, either alone or in combination with spleen size[50-52] is associated with CSPH and esophageal varices, and is the single most commonly reported non-invasive sign of portal hypertension. Nonetheless, there is not any established cut-off for platelet count able to accurately diagnose or exclude CSPH in patients with cirrhosis[13].

Ultrasound (US) is the first-line imaging technique used in patients with suspected cirrhosis and portal hypertension, since it is cheap, repeatable, and allows direct visualization of the anatomical changes induced by PH[53,54]. US signs of PH in cirrhosis are multiple[55,56]; overall, the sensitivity of the technique is moderate, but its specificity is above 90%. Hence, the presence of one or more US signs of PH allows to diagnose CSPH, but the absence of signs do not exclude CSPH, suggesting that it should be investigated by more sensitive techniques (*e.g.*, HVPG measurement). Splenomegaly, defined as an increase in spleen diameter above 12 cm, is among the most commonly reported signs. It is sensitive but poorly specific, while porto-collateral vessels have a low sensitivity but 100% specificity for the diagnosis of CSPH. This last sign can be therefore considered a reliable surrogate of PH if detected either on US or on CT/MR imaging.

Liver stiffness (LS) measured by transient elastography (Fibroscan®) is a well-accepted objective non-invasive method to reliably estimate liver fibrosis[57]. It has been shown that LS and HVPG show a good correlation in patients with compensated cirrhosis[13,58]. LS cut-off for the detection of CSPH varies across studies, but it is widely accepted that values above 21 kPa have a high specificity for CSPH. This has been recently confirmed by a longitudinal study using clinical endpoints that showed that HVPG ⩾ 10 mmHg and LS > 21 kPa equally predict clinical decompensation in patients with compensated cirrhosis at baseline[59], making LS the most accurate method so far for predicting CSPH. Preliminary data suggests that spleen stiffness has a better correlation with HVPG than LS, but data are still limited[60].

The combination of different non-invasive methods offers potential benefits by integrating complementary information. In a recent study by our group where HVPG was used as the gold standard for diagnosing CSPH, the combination of LS, platelet count and spleen size either as LSPS[23] or as a newly calculated PH risk score improved the accuracy of LS alone for detecting CSPH, and allowed a correct diagnosis in 86% of cases[13].

The EASL[9] and AASLD[10] practice guidelines for HCC management recommend evaluation of portal hypertension prior treatment decision in HCC patients with a single tumour. For this purpose, HVPG measurement is the best available option and should be considered the standard-of-care. However, it cannot be routinely performed in all hospitals. Platelet count below 100×10^3/mL is often used to identify CSPH, especially when associated with splenomegaly[13]. In this regard, it should be underscored that both platelet count and spleen size are inaccurate for diagnosing CSPH in this specific setting[13]. Specifically, while in patients with both signs CSPH is highly probable, the absence of thrombocytopenia and/or splenomegaly cannot exclude CSPH. This has been recently confirmed in a prospective study in patients undergoing surgery for HCC including HVPG measurement[14] and reinforces the notion that more objective and accurate methods are still needed to accurately diagnose or exclude CSPH in patients with potentially resectable HCC.

Given that liver stiffness by transient elastography is currently considered the single most reliable non-invasive surrogate marker of PH, researchers from Eastern and Western countries evaluated its accuracy to predict CSPH and PH-related complication after surgery for HCC. A study including 72 patients found that LS had a good accuracy (area under receiver operating characteristic curve 0.824) in discriminating which patients would decompensate after surgery, being superior than the test usually used in Eastern countries (indocyanine green clearance at 15 min)[61]. Our group tested LS accuracy in the diagnosis of CSPH versus the gold-standard measurement of HVPG in a series of 90 patients with Child A cirrhosis and potentially resectable HCC[24]. In the 79 patients in whom LS was feasible (88% of applicability), the correlation with HVPG was lower than previously published in patients without HCC, suggesting that factors related to tumor location might interfere with LS measurements[24]. Nonetheless, results demonstrated that a cut-off of 13.6 kPa was 90% sensitive to detect CSPH, while the 21.1 kPa cutoff was highly specific. In other words, CSPH could be reasonably excluded in patients with LS < 13.6 kPa, and reliably diagnosed in those with LS ≥ 21.1 kPa. This simple rule could eventually decrease the need for HVPG measurement by half, being confined to those patients with intermediate LS levels (between 13.6-21.1 kPa) and those with unreliable measurements (*e.g.*, obesity, *etc.*). Furthermore, combination of LS with platelet count and spleen diameter has the potential of reducing the number of patients in this "grey zone", allowing to correctly diagnose CSPH in 85% of patients, although these findings need validation in independent series.

MOLECULAR PROGNOSTIC BIOMARKERS IN SMALL HCC

There is a pressing need to incorporate prognostic and predictive biomarkers in HCC management. Genome-wide expression studies have been applied in the HCC field trying to provide physicians with better tools to characterize early lesions and even to optimize patient selection for personalize therapies.

Different studies indicate that HCC can be broadly classified according to its molecular features in two major subclasses[62]. One is characterized by molecular signals of proliferation and cell cycle, usually enriched in TP53 inactivation; whereas the second subclass is characterized by *CTNNB1* mutations and enrichment in WNT target genes *GLUL*, *LGR5*, and *LECT2*. The subclass related to proliferation can be been further divided according to the activation of other cascades such as transforming growth factor-beta signaling, insulin-like growth factor[63], Notch[64], *etc.*

Besides molecular classification, a number of studies have reported gene signatures able to predict prognosis in HCC (thoroughly reviewed elsewhere[62]), not only generated from the tumor but also from the adjacent non-tumoral cirrhotic tissue. Recently an integrated prognostic model that combines genomic information from both the tumor and the adjacent tissue together with clinical-pathologic data was able to accurately predict outcome in patients with a single nodule early HCC[65]. Despite all these data from molecular profiling studies, gene signatures have not been yet incorporated clinical practice guidelines[62].

REFERENCES

1 **Jemal A**, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009; **59**: 225-249 [PMID: 19474385]

2 **Seitz HK**, Stickel F. Risk factors and mechanisms of hepatocarcinogenesis with special emphasis on alcohol and oxidative stress. *Biol Chem* 2006; **387**: 349-360 [PMID: 16606331]

3 **Llovet JM**, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology* 1999; **30**: 1434-1440 [PMID: 10573522]

4 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514]

5 **El-Serag HB**. Hepatocellular carcinoma. *N Engl J Med* 2011; **365**: 1118-1127 [PMID: 21992124]

6 **Kudo M**. Review of 4th Single Topic Conference on HCC. Hepatocellular carcinoma: International consensus and controversies. *Hepatol Res* 2007; **37** Suppl 2: S83-S87 [PMID: 17877501]

7 **Roskams T**. Anatomic pathology of hepatocellular carcinoma: impact on prognosis and response to therapy. *Clin Liver Dis* 2011; **15**: 245-259, vii-x [PMID: 21689611]

8 **Kojiro M**, Roskams T. Early hepatocellular carcinoma and dysplastic nodules. *Semin Liver Dis* 2005; **25**: 133-142 [PMID: 15918142]

9 European Association For The Study Of The Liver, European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 908-943 [PMID: 22424438]

10 **Bruix J**, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020-1022 [PMID: 21374666]

11 **Forner A**, Bruix J. East meets the West--portal pressure predicts outcome of surgical resection for hepatocellular carcinoma. *Nat Clin Pract Gastroenterol Hepatol* 2009; **6**: 14-15 [PMID: 18981995]
12 **Bruix J**, Castells A, Bosch J, Feu F, Fuster J, Garcia-Pagan JC, Visa J, Bru C, Rodés J. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. *Gastroenterology* 1996; **111**: 1018-1022 [PMID: 8831597]
13 **Berzigotti A**, Seijo S, Arena U, Abraldes JG, Vizzutti F, García-Pagán JC, Pinzani M, Bosch J. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. *Gastroenterology* 2013; **144**: 102-111.e1 [PMID: 23058320]
14 **Boleslawski E**, Petrovai G, Truant S, Dharancy S, Duhamel A, Salleron J, Deltenre P, Lebuffe G, Mathurin P, Pruvot FR. Hepatic venous pressure gradient in the assessment of portal hypertension before liver resection in patients with cirrhosis. *Br J Surg* 2012; **99**: 855-863 [PMID: 22508371]
15 **Capussotti L**, Ferrero A, Viganò L, Muratore A, Polastri R, Bouzari H. Portal hypertension: contraindication to liver surgery? *World J Surg* 2006; **30**: 992-999 [PMID: 16736327]
16 **Cescon M**, Colecchia A, Cucchetti A, Peri E, Montrone L, Ercolani G, Festi D, Pinna AD. Value of transient elastography measured with FibroScan in predicting the outcome of hepatic resection for hepatocellular carcinoma. *Ann Surg* 2012; **256**: 706-712; discussion 712-713 [PMID: 23095613]
17 **Chen X**, Zhai J, Cai X, Zhang Y, Wei L, Shi L, Wu D, Shen F, Lau WY, Wu M. Severity of portal hypertension and prediction of postoperative liver failure after liver resection in patients with Child-Pugh grade A cirrhosis. *Br J Surg* 2012; **99**: 1701-1710 [PMID: 23132418]
18 **Cucchetti A**, Ercolani G, Vivarelli M, Cescon M, Ravaioli M, Ramacciato G, Grazi GL, Pinna AD. Is portal hypertension a contraindication to hepatic resection? *Ann Surg* 2009; **250**: 922-928 [PMID: 19855258]
19 **Figueras J**, Llado L, Ruiz D, Ramos E, Busquets J, Rafecas A, Torras J, Fabregat J. Complete versus selective portal triad clamping for minor liver resections: a prospective randomized trial. *Ann Surg* 2005; **241**: 582-590 [PMID: 15798459]
20 **Giuliante F**, Ardito F, Pinna AD, Sarno G, Giulini SM, Ercolani G, Portolani N, Torzilli G, Donadon M, Aldrighetti L, Pulitanò C, Guglielmi A, Ruzzenente A, Capussotti L, Ferrero A, Calise F, Scuderi V, Federico B, Nuzzo G. Liver resection for hepatocellular carcinoma ≤3 cm: results of an Italian multicenter study on 588 patients. *J Am Coll Surg* 2012; **215**: 244-254 [PMID: 22634119]
21 **Imamura H**, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S, Sugawara Y, Minagawa M, Takayama T, Kawasaki S, Makuuchi M. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol* 2003; **38**: 200-207 [PMID: 12547409]
22 **Ishizawa T**, Hasegawa K, Kokudo N, Sano K, Imamura H, Beck Y, Sugawara Y, Makuuchi M. Risk factors and management of ascites after liver resection to treat hepatocellular carcinoma. *Arch Surg* 2009; **144**: 46-51 [PMID: 19153324]
23 **Kim BK**, Han KH, Park JY, Ahn SH, Kim JK, Paik YH, Lee KS, Chon CY, Kim do Y. A liver stiffness measurement-based, noninvasive prediction model for high-risk esophageal varices in B-viral liver cirrhosis. *Am J Gastroenterol* 2010; **105**: 1382-1390 [PMID: 20087336]
24 **Llop E**, Berzigotti A, Reig M, Erice E, Reverter E, Seijo S, Abraldes JG, Bruix J, Bosch J, García-Pagan JC. Assessment of portal hypertension by transient elastography in patients with compensated cirrhosis and potentially resectable liver tumors. *J Hepatol* 2012; **56**: 103-108 [PMID: 21827733]
25 **Ishizawa T**, Hasegawa K, Aoki T, Takahashi M, Inoue Y, Sano K, Imamura H, Sugawara Y, Kokudo N, Makuuchi M. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. *Gastroenterology* 2008; **134**: 1908-1916 [PMID: 18549877]
26 **Llovet JM**, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; **362**: 1907-1917 [PMID: 14667750]
27 **Mazzaferro V**, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699 [PMID: 8594428]
28 **Livraghi T**, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, Rossi S. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? *Hepatology* 2008; **47**: 82-89 [PMID: 18008357]
29 **Castells A**, Bruix J, Bru C, Fuster J, Vilana R, Navasa M, Ayuso C, Boix L, Visa J, Rodés J. Treatment of small hepatocellular carcinoma in cirrhotic patients: a cohort study comparing surgical resection and percutaneous ethanol injection. *Hepatology* 1993; **18**: 1121-1126 [PMID: 8225217]
30 **Livraghi T**, Bolondi L, Lazzaroni S, Marin G, Morabito A, Rapaccini GL, Salmi A, Torzilli G. Percutaneous ethanol injection in the treatment of hepatocellular carcinoma in cirrhosis. A study on 207 patients. *Cancer* 1992; **69**: 925-929 [PMID: 1310435]
31 **Lin SM**, Lin CJ, Lin CC, Hsu CW, Chen YC. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. *Gut* 2005; **54**: 1151-1156 [PMID: 16009687]
32 **Lin SM**, Lin CJ, Lin CC, Hsu CW, Chen YC. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma & lt; or =4 cm. *Gastroenterology* 2004; **127**: 1714-1723 [PMID: 15578509]
33 **Lencioni RA**, Allgaier HP, Cioni D, Olschewski M, Deibert P, Crocetti L, Frings H, Laubenberger J, Zuber I, Blum HE, Bartolozzi C. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. *Radiology* 2003; **228**: 235-240 [PMID: 12759473]
34 **Brunello F**, Veltri A, Carucci P, Pagano E, Ciccone G, Moretto P, Sacchetto P, Gandini G, Rizzetto M. Radiofrequency ablation versus ethanol injection for early hepatocellular carcinoma: A randomized controlled trial. *Scand J Gastroenterol* 2008; **43**: 727-735 [PMID: 18569991]
35 **Shiina S**, Teratani T, Obi S, Sato S, Tateishi R, Fujishima T, Ishikawa T, Koike Y, Yoshida H, Kawabe T, Omata M. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. *Gastroenterology* 2005; **129**: 122-130 [PMID: 16012942]
36 **Lencioni R**, Cioni D, Crocetti L, Franchini C, Pina CD, Lera J, Bartolozzi C. Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. *Radiology* 2005; **234**: 961-967 [PMID: 15665226]
37 **Omata M**, Tateishi R, Yoshida H, Shiina S. Treatment of hepatocellular carcinoma by percutaneous tumor ablation methods: Ethanol injection therapy and radiofrequency ablation. *Gastroenterology* 2004; **127**: S159-S166 [PMID: 15508080]
38 **Sala M**, Llovet JM, Vilana R, Bianchi L, Solé M, Ayuso C, Brú C, Bruix J. Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. *Hepatology* 2004; **40**: 1352-1360 [PMID: 15565564]
39 **Lau WY**, Leung TW, Yu SC, Ho SK. Percutaneous local ablative therapy for hepatocellular carcinoma: a review and look into the future. *Ann Surg* 2003; **237**: 171-179 [PMID: 12560774]
40 **Finkelstein SD**, Marsh W, Demetris AJ, Swalsky PA, Sasatomi E, Bonham A, Subotin M, Dvorchik I. Microdissection-based allelotyping discriminates de novo tumor from intrahepatic spread in hepatocellular carcinoma. *Hepatology* 2003; **37**: 871-879 [PMID: 12668980]
41 **Bosch J**, Abraldes JG, Berzigotti A, García-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. *Nat Rev Gastroenterol Hepatol* 2009; **6**: 573-582 [PMID:

19724251]
42 **Gluud C**, Brok J, Gong Y, Koretz RL. Hepatology may have problems with putative surrogate outcome measures. *J Hepatol* 2007; **46**: 734-742 [PMID: 17316871]
43 **Groszmann RJ**, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, Escorsell A, Garcia-Pagan JC, Patch D, Matloff DS, Gao H, Makuch R. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med* 2005; **353**: 2254-2261 [PMID: 16306522]
44 **Ripoll C**, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, Escorsell A, Garcia-Pagan JC, Makuch R, Patch D, Matloff DS, Bosch J. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology* 2007; **133**: 481-488 [PMID: 17681169]
45 **Ripoll C**, Groszmann RJ, Garcia-Tsao G, Bosch J, Grace N, Burroughs A, Planas R, Escorsell A, Garcia-Pagan JC, Makuch R, Patch D, Matloff DS. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. *J Hepatol* 2009; **50**: 923-928 [PMID: 19303163]
46 **Gluud C**, Henriksen JH, Nielsen G. Prognostic indicators in alcoholic cirrhotic men. *Hepatology* 1988; **8**: 222-227 [PMID: 3258578]
47 **Stanley AJ**, Robinson I, Forrest EH, Jones AL, Hayes PC. Haemodynamic parameters predicting variceal haemorrhage and survival in alcoholic cirrhosis. *QJM* 1998; **91**: 19-25 [PMID: 9519209]
48 **Braillon A**, Cales P, Valla D, Gaudy D, Geoffroy P, Lebrec D. Influence of the degree of liver failure on systemic and splanchnic haemodynamics and on response to propranolol in patients with cirrhosis. *Gut* 1986; **27**: 1204-1209 [PMID: 3781335]
49 **Berzigotti A**, Gilabert R, Abraldes JG, Nicolau C, Bru C, Bosch J, García-Pagan JC. Noninvasive prediction of clinically significant portal hypertension and esophageal varices in patients with compensated liver cirrhosis. *Am J Gastroenterol* 2008; **103**: 1159-1167 [PMID: 18477345]
50 **Giannini E**, Botta F, Borro P, Risso D, Romagnoli P, Fasoli A, Mele MR, Testa E, Mansi C, Savarino V, Testa R. Platelet count/spleen diameter ratio: proposal and validation of a non-invasive parameter to predict the presence of oesophageal varices in patients with liver cirrhosis. *Gut* 2003; **52**: 1200-1205 [PMID: 12865282]
51 **Schepis F**, Cammà C, Niceforo D, Magnano A, Pallio S, Cinquegrani M, D'amico G, Pasta L, Craxì A, Saitta A, Raimondo G. Which patients with cirrhosis should undergo endoscopic screening for esophageal varices detection? *Hepatology* 2001; **33**: 333-338 [PMID: 11172334]
52 **Zaman A**, Hapke R, Flora K, Rosen HR, Benner K. Factors predicting the presence of esophageal or gastric varices in patients with advanced liver disease. *Am J Gastroenterol* 1999; **94**: 3292-3296 [PMID: 10566732]
53 **Berzigotti A**, Zoli M, Bru C, Gilabert R, de Franchis R. Ultrasound in the non-invasive evaluation of fibrosis and portal hypertension. In: Portal Hypertension V: Proceedings of the Fifth Baveno International Consensus Workshop. Wiley-Blackwell, 2010: 28-36
54 **Berzigotti A**. Transient elastography and prognosis of cirrhosis. *Hepatology* 2012; **55**: 1629-1631 [PMID: 22517548]
55 **Berzigotti A**, Piscaglia F. Ultrasound in portal hypertension--part 1. *Ultraschall Med* 2011; **32**: 548-568; quiz 569-571 [PMID: 22161554]
56 **Berzigotti A**, Piscaglia F. Ultrasound in portal hypertension--part 2--and EFSUMB recommendations for the performance and reporting of ultrasound examinations in portal hypertension. *Ultraschall Med* 2012; **33**: 8-32; quiz 30-31 [PMID: 22322479]
57 **Friedrich-Rust M**, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, Herrmann E. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. *Gastroenterology* 2008; **134**: 960-974 [PMID: 18395077]
58 **Castera L**, Pinzani M, Bosch J. Non invasive evaluation of portal hypertension using transient elastography. *J Hepatol* 2012; **56**: 696-703 [PMID: 21767510]
59 **Robic MA**, Procopet B, Métivier S, Péron JM, Selves J, Vinel JP, Bureau C. Liver stiffness accurately predicts portal hypertension related complications in patients with chronic liver disease: a prospective study. *J Hepatol* 2011; **55**: 1017-1024 [PMID: 21354450]
60 **Colecchia A**, Montrone L, Scaioli E, Bacchi-Reggiani ML, Colli A, Casazza G, Schiumerini R, Turco L, Di Biase AR, Mazzella G, Marzi L, Arena U, Pinzani M, Festi D. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. *Gastroenterology* 2012; **143**: 646-654 [PMID: 22643348]
61 **Kim SU**, Ahn SH, Park JY, Kim do Y, Chon CY, Choi JS, Kim KS, Han KH. Prediction of postoperative hepatic insufficiency by liver stiffness measurement (FibroScan((R))) before curative resection of hepatocellular carcinoma: a pilot study. *Hepatol Int* 2008; **2**: 471-477 [PMID: 19669322]
62 **Hoshida Y**, Toffanin S, Lachenmayer A, Villanueva A, Minguez B, Llovet JM. Molecular classification and novel targets in hepatocellular carcinoma: recent advancements. *Semin Liver Dis* 2010; **30**: 35-51 [PMID: 20175032]
63 **Tovar V**, Alsinet C, Villanueva A, Hoshida Y, Chiang DY, Solé M, Thung S, Moyano S, Toffanin S, Mínguez B, Cabellos L, Peix J, Schwartz M, Mazzaferro V, Bruix J, Llovet JM. IGF activation in a molecular subclass of hepatocellular carcinoma and pre-clinical efficacy of IGF-1R blockage. *J Hepatol* 2010; **52**: 550-559 [PMID: 20206398]
64 **Villanueva A**, Alsinet C, Yanger K, Hoshida Y, Zong Y, Toffanin S, Rodriguez-Carunchio L, Solé M, Thung S, Stanger BZ, Llovet JM. Notch signaling is activated in human hepatocellular carcinoma and induces tumor formation in mice. *Gastroenterology* 2012; **143**: 1660-1669.e7 [PMID: 22974708 DOI: 10.1053/j.gastro.2012.09.002]
65 **Villanueva A**, Hoshida Y, Battiston C, Tovar V, Sia D, Alsinet C, Cornella H, Liberzon A, Kobayashi M, Kumada H, Thung SN, Bruix J, Newell P, April C, Fan JB, Roayaie S, Mazzaferro V, Schwartz ME, Llovet JM. Combining clinical, pathology, and gene expression data to predict recurrence of hepatocellular carcinoma. *Gastroenterology* 2011; **140**: 1501-1512.e2 [PMID: 21320499]
66 **Huang GT**, Lee PH, Tsang YM, Lai MY, Yang PM, Hu RH, Chen PJ, Kao JH, Sheu JC, Lee CZ, Chen DS. Percutaneous ethanol injection versus surgical resection for the treatment of small hepatocellular carcinoma: a prospective study. *Ann Surg* 2005; **242**: 36-42 [PMID: 15973099]
67 **Huang J**, Yan L, Cheng Z, Wu H, Du L, Wang J, Xu Y, Zeng Y. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. *Ann Surg* 2010; **252**: 903-912 [PMID: 21107100]
68 **Feng K**, Yan J, Li X, Xia F, Ma K, Wang S, Bie P, Dong J. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. *J Hepatol* 2012; **57**: 794-802 [PMID: 22634125]

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