CLINICS

EDITORIAL

Is hepatic venous pressure gradient assessment required before liver resection in patients with cirrhosis and hepatocellular carcinoma?

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The importance of the hepatic venous pressure gradient (HVPG) in selecting patients with hepatocellular carcinoma (HCC) for liver resection (LR) has been somewhat controversial. Recently, Boleslawski et al. prospectively evaluated a cohort of 40 patients undergoing LR for HCC; the authors aimed to identify the impact of HVPG values and clinical signs of portal hypertension (esophageal varices or splenomegaly with a platelet count $<100{,}000/mm^3$) on postoperative outcomes (1). The study showed that liver dysfunction and 90-day postoperative mortality rates were associated with high HVPG values ($p = 0.017$ and 0.026, respectively). In contrast, the presence of clinical features of portal hypertension was not associated with either liver dysfunction or short-term mortality. The authors concluded that the HVPG should be measured routinely in HCC patients prior to LR. Clinical practice guidelines from the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) suggest that clinical parameters can be used as an alternative to HPVG in determining the presence of clinically relevant portal hypertension (2,3). Consequently, HVPG assessment may not be necessary in all LR candidates (4). Although the Boleslawski et al. study examined an important aspect of LR for HCC patients, some concerns should be addressed.

There is no clear maximum tumor size that contraindicates LR in HCC patients with a single nodule (2,3). Nevertheless, in a patient with well-preserved liver function and a single tumor up to 5 cm, the presence of portal hypertension is accepted as an adverse prognostic factor that is associated with reduced and long-term patient survival (5,6). In 1996, Bruix et al. first reported the negative impact of significant portal hypertension on liver resection outcomes (5). Twenty-nine cirrhotic Child-Turcotte-Pugh (CPT) class A patients who underwent LR were evaluated to determine the role of increased portal pressure in developing postoperative hepatic decompensation. Eleven of the 29 patients developed persistent liver decompensation within the first three months after surgery, and HVPG was the only independent factor that predicted hepatic decompensation in a multivariate analysis ($p<0.001$). Subsequently, the same researchers updated their results, suggesting that either HVPG or clinical signs of portal hypertension could be used to select HCC patients for resection or liver transplantation (6). Note that patients with a single tumor >5 cm do not fulfill the Milan criteria, and liver transplantation is not usually considered a treatment alternative (2,3,7). Therefore, the presence of portal hypertension as an absolute criterion for selecting patients for liver transplantation, rather than resection, is of most relevance to the subgroup of patients who could undergo either resection or transplantation. Given the limited efficacy of other treatment options for this patient subset, such as transarterial chemoembolization, patients with a single tumor >5 cm may still be best served by liver resection, even in the presence of portal hypertension. The study by Boleslawski et al. did not mention tumor number or size in the 40 enrolled patients, and this information may aid in interpreting their data and conclusions. Note that in their series, not all of the patients performed poorly (despite liver resection in the presence of a HVPG >10 mmHg), and portal hypertension clinically-based (PH-CB) was not predictive of patient outcomes.

In light of the uncertainties surrounding the role of portal hypertension in selecting HCC patients for liver resection, we recently undertook a multicenter (in Australia, Spain, and Brazil), exploratory analysis of 105 CPT A HCC patients (with a single nodule ≤5 cm on imaging) who were treated with primary liver resection (unpublished data). After a median follow up of 51 months (range, 1–159 months), the 1-, 3-, and 5-year survival rates were 97%, 83%, and 66%, respectively. As in other studies, significant portal hypertension was defined as having an HVPG ≥10 mmHg or the presence of gastroesophageal varices, splenomegaly (spleen length ≥12 cm) with a platelet count $<100{,}000/mm^3$, or the need for diuretics to control ascites. PH-CB was defined with the same criteria but without the HVPG variable. No pre-operative characteristic predicted the likelihood of survival after assessing all of the variables recommended by the Panel of Experts in HCC-Design Clinical Trials (7). In other words, our results suggest that liver resection for CPT A HCC patients with a single tumor ≤5 cm offers survival rates similar to liver transplantation, independent of any pre-operative characteristics (8).

We have summarized the published studies evaluating liver resection for patients with cirrhosis and HCC (Table 1). It is clear that the data regarding the prognostic factors for HCC

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No potential conflict of interest was reported.

DOI: 10.6061/clinics/2013(04)01

Table 1 - Results of a series evaluating liver resection in patients with hepatocellular carcinoma and cirrhosis.

Author, year	Design	Tumor Assessment	Inclusion Criteria	Patients	Survival (%)		Comments
					1-year	5-year	
Llovet et al., 1999	Retrospective	Radiology	Single nodule up to 5 cm, well-preserved liver function.	n = 77	85	51	SPH and BL were the factors associated with survival. The subset of patients with neither SPH nor BL ≥1 mg/dL had a 5-year survival rate of 74%. This study compared the results of 2 independent arms of HCC patients undergoing LR or LT.
Chiappa et al., 2000	Retrospective	Pathology	Not defined	n = 51	89	53 at 3 years	After a median follow-up of 28 months, tumor recurrence occurred in 45% of cases. Microvascular invasion and symptomatic tumors were associated with poor long-term survival.
Grazi et al., 2001	Retrospective	Pathology	CPT A or B without ascites, HE, or esophageal varices.	n = 264	N/A	41	Patients who underwent resection after 1992 (n = 157) had higher 5-year survival rates than the remainder (49% *versus* 32%, $p<0.05$).
Yamamoto et al., 2001	Retrospective	Radiology	Without ascites or jaundice; >3 cm and >3 nodules.	n = 58	96	61	This study was primarily designed to compare resection (n = 58) to PEI (n = 39). The survival rates were similar between the groups ($p = 0.96$), although the cohorts had different baseline characteristics.
Poon et al., 2002	Prospective	Pathology	Neither extrahepatic spread nor macrovascular invasion.	n = 206	Group 1 = 70 Group 2 = 161	Group A = 33 Group B = 44	This study was primarily designed to compare extended LR (Group 1, n = 45) to lesser extent liver resection (Group 2, n = 161). Eighty-six percent of the patients had hepatitis B cirrhosis.
Ercolani et al., 2003	Retrospective	Pathology	Not defined	n = 224	83	42	Ninety-eight patients received TACE prior to LR. Patients with a single nodule had higher long-term survival in the multivariate analysis.
Ferrero et al., 2005	Retrospective	Pathology	Not defined	n = 241	≤70 yrs = 74 >70 yrs = 81	≤70 yrs = 32 >70 yrs = 48	This study was primarily designed to compare LR according to age (≤70 yrs, n = 177) and (>70 yrs, n = 64). The survival rates were similar between the groups ($p = 0.081$).
Wu et al., 2005	Retrospective	Pathology	Absence of vein invasion or extrahepatic spread	n = 426	N/A N/A	Group 1 = 61 Group 2 = 46	This study was primarily designed to compare LR according to the period (1991-1996, n = 161, Group 1) and (1997 – 2002, n = 265, Group 2). The 5-yeear survival rates were higher in Group 2 ($p<0.001$).
Margarit et al., 2005	Retrospective	Radiology	CPT A, single nodule up to 5 cm, <70 yrs, normal BL, without SPH.	n = 73	LR = 92 LT = 78	LR = 70 LT = 65	This study was primarily designed to compare LR (n = 37) to LT (n = 36). TACE prior to LR and LT was performed in selected cases.
Capussotti et al., 2006	Retrospective	Pathology	Not defined	n = 217	N/A	SPH = 29 No SPH = 39	Patients with SPH had poor long-term survival rates ($p = 0.020$); however, when considering only CPT A patients, the survival rates were similar between the groups ($p = 0.503$).
Taura et al., 2007	Retrospective	Pathology	MC	CPT A = 129 CPT B = 37	N/A N/A	54 28	This study included a third subgroup of non-cirrhotic patients (n = 127). The presence of cirrhosis was associated with lower overall survival and a greater risk of recurrence.
Ishizawa et al., 2008	Retrospective	Pathology	Depending on ascites, BL, and ICGR15.	n = 434	N/A	SPH = 56 No SPH = 71	This study was primarily designed to compare patients with SPH (n = 136) to those without PH (n = 250). CPT B patients had a 5-year survival rate of 19%. The results shown in the table correspond to the subset of CPT A patients. Eighteen percent of the enrolled cases had no cirrhosis.
Park et al., 2009	Retrospective	Radiology	CPT A, MC	n = 213	92	69	Patients were followed for 34 (1–145) months. Six patients underwent salvage living donor LT. The overall survival between patients with a single nodule and 2-3 nodules separately were not shown.

Table 1 - Continued.

Author, year	Design	Tumor Assessment	Inclusion Criteria	Patients	Survival (%)		Comments
					1-year	5-year	
Santambrogio et al., 2009	Retrospective	Radiology	Single nodule ≤5 cm; CPT A; resection of <2 segments.	LRFA = 74 LR = 78	LRFA = 88 LR = 93	LRFA = 41 LR = 54	This study was primarily designed to compare LR with LRFA. Patients were selected for 1 of these alternatives on the basis of tumor location. The survival rates were similar between the 2 forms of LR.
Zhou et al., 2010	Retrospective	Radiology	MC; CPT A and B.	n = 1,018 n = 89	N/A N/A	LR = 70% at 4 years LT = 87% at 4 years	This study was primarily designed to compare LR with LT. LT had higher survival rates than LR. However, patients with tumors with a size-plus-number of up to 4 or absence of microvascular invasion had similar long-term survival between the groups.
Sapisochin et al., 2010	Retrospective	Radiology	CPT A or B; single HCC; no extrahepatic spread nor macrovascular invasion.	n = 100	59	52	This study was primarily designed to ascertain the outcome of LT due to HCC in patients who had undergone previous LR (n = 17). It was shown that patients with recurrence within the first year after LR had a poor prognosis after salvage LT.
Abdel-Wahab et al., 2010	Retrospective	Pathology	BL <2 mg/dL, albumin >3 g/dL, prothrombin activity >60% without ascites, portal vein thrombosis or extrahepatic spread.	n = 175	72	21	There was no restriction regarding tumor number and size. After a median follow-up of 24 months, 78 cases developed tumor recurrence.
Lee et al., 2010	Retrospective	Radiology	CPT A or B, BL <3 mg/dL, controllable ascites.	n = 130	80	52	This study was primarily designed to compare LR with LT (n = 78). It was concluded that LT should be the primary option in patients within the MC, whereas LR should be the first treatment in patients beyond the MC.
Huang et al., 2011	Retrospective	Pathology	CPT A or B, no extrahepatic spread or nodal involvement; any tumor size and number.	n = 77	78	56 in 3 years	Eighty percent of the enrolled patients had cirrhosis caused by hepatitis B; the survival rates at 1 and 3 years were 87%, and 75%, respectively ($p = 0.002$) in patients with nodules smaller than 5 cm.
Sapisochin et al., 2012	Retrospective	Radiology	Single nodule ≤5 cm; no portal hypertension and normal bilirubin	n = 95	82	60 33 at 10 years	This study was primarily designed to compare LR (n = 95) with LT (n = 122) on an intention-to-treat basis. The authors concluded that at 5 years survival was equivalent; nevertheless, LT achieved a better outcome at 10 years. Moreover, when they compared patients resected with early HCC (tumors ≤2 cm) with LT, the 10-year survival was similar.
Boleslawski et al., 2012	Prospective	N/A	N/A	n = 40	N/A	N/A	This study was primarily designed to evaluate the impact of portal hypertension on short-term survival and morbidities post-LR; see text for details.
Silva et al., 2012	Retrospective	Radiology	CPT A, single nodule ≤5 cm	n = 105	85	66	No pre-operative characteristics were associated with patient survival; see text for further information. This study was based on the intention-to-treat principle.

Abbreviations: SPH, significant portal hypertension; BL, serum total bilirubin; HCC, hepatocellular carcinoma; LR, liver resection; LT, liver transplantation; CPT, Child-Pugh-Turcotte; N/A, not available; HE, hepatic encephalopathy; PEI, percutaneous ethanol injection; TACE, transarterial chemoembolization; ICGR15, indocyanine green retention rate at 15 minutes; MC, Milan criteria; LRFA, laparoscopic radiofrequency ablation.

patients undergoing liver resection are scarce. Current recommendations for patient selection for liver resection *versus* liver transplantation for tumors ≤5 cm are still based on the original Barcelona group publication, which was based on a retrospective analysis of a case series from the 1990s (5). Note that given the limitations of retrospective studies, the robustness of evidence supporting this finding must be validated following evidenced-based ranking systems (9). Basing recommendations on the results of liver resection performed in the 1990s ignores recent improvements in the perioperative care of cirrhotic patients (10). These recommendations may also limit access to liver resection for patients who have no or limited access to liver transplantation.

In conclusion, further well-designed trials are warranted to evaluate the role of significant portal hypertension in predicting liver resection outcomes for HCC patients. Nevertheless, until further well-designed prospective studies are undertaken, the recommendations of the EASL–HCC Clinical Practice Guidelines should remain in place.

AUTHOR CONTRIBUTIONS

All of the authors declare that they contributed equally to the text.

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