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EDITORIAL – HEPATOBILIARY TUMORS

When Does Invasion Mean the War is Lost?

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The significance of macrovascular invasion (MVI) in hepatocellular carcinoma (HCC) is ill defined. Although the Barcelona Clinic Liver Cancer Classification System classifies disease associated with MVI as stage C and recommends that patients with MVI be offered palliative therapy with the oral multikinase inhibitor sorafenib, several centers have reported successful liver resection with good outcomes in patients with MVI.[1] The paper by Roayaie et al.[2] provides an excellent opportunity to revisit the significance of MVI in HCC. We congratulate the authors for their thorough evaluation of their results, critical discussion of their data, and comprehensive summary and analysis of the available relevant literature.

The authors performed a retrospective analysis of 165 patients with Child's class A cirrhosis and MVI treated with primary hepatic resection during the period from 1992 to 2010. Median survival time after surgery was 13.1 months, and the 5-year survival rate was 14 %. These outcomes compare favorably to the 8-month median survival of patients with MVI who received sorafenib during the important SHARP trial (108 patients, 36 % of the patients in the sorafenib group).[3] In their multivariate analysis, Roayaie et al.[2] determined that alfa-fetoprotein level greater than 30 ng/mL, tumor size greater than 7 cm, and more extensive vascular invasion were independent predictors of worse overall survival. Furthermore, hepatic vein or inferior vena cava invasion was associated with significantly worse overall survival following resection (median 4.7 months) than was portal venous invasion (median 9.2 months). Possible reasons for the poor outcomes of patients with hepatic vein or inferior vena cava invasion undergoing resection might be ready access of the tumor to the systemic venous circulation or the high morbidity of the surgery itself.

A question that could have been addressed in the paper in more detail is whether there are shades of gray when it comes to portal venous invasion by HCC. We think the answer is "yes." Ikai et al.[4] published a paper in 2003 that showed that there are survival differences according to the order of portal branch involved, a parameter that allows accurate prognostication (Fig. 1). The Liver Cancer Study Group of Japan has adopted and incorporated this concept. Therefore, MVI of the portal vein is helpful for determining outcome, as shown by Roayaie et al.,[2] but might be defined more precisely as a discrete variable (tumor thrombus in first-, second-, or third-order branch) than as a qualitative variable (presence or absence of MVI).

An issue raised by the authors is the 60 % rate of detection of MVI on preoperative imaging. Although the long time interval covered by the study (1992–2010) saw advances in operative techniques (the reported mortality rate of 28 % for patients with hepatic vein or inferior vena cava involvement might be lower today) and the 2005 approval of sorafenib by the Food and Drug Administration, the preoperative detection sensitivity and specificity of Vp1-4 MVI might still only be around 70 and 80 % respectively.[5] Preoperative detection of major vascular invasion (Vp3) is important to determine the need for preoperative transarterial chemoembolization (TACE). Roayaie et al.[2] were surprised by the results of the study by Minagawa et al.[6], in which 18 patients undergoing TACE plus liver resection were compared to 27 patients who did not undergo hepatectomy. This study was conducted at a center with specialized expertise in a cohort of patients

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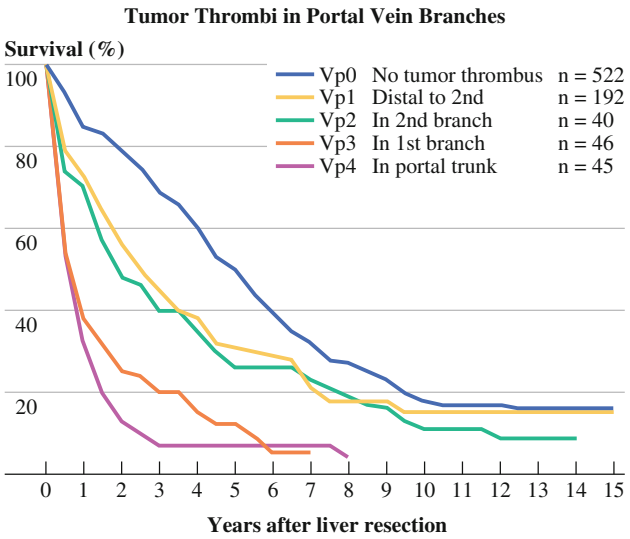

FIG. 1 Survival of patients with portal vein invasion depends on which order of portal vein branch is involved (adapted from Ikai et al.[4])

with advanced first-order portal branch involvement (Vp3), and the 5-year survival rate after hepatectomy was 42 %. In our experience with patients with major vascular TACE can solidify the tumor thrombus and this may prevent tumor dissemination in the FLR and reduce early intrahepatic recurrence. Several studies from Asia have been published on the strategy of TACE followed by liver resection. Although the degree of vascular invasion often not detailed in the publication, some reports describe the use of TACE to convert HCC from unresectable to resectable.[7,8] This strategy should be considered in experienced centers.

Some of the parameters that might be useful for patient stratification are available in the pathology report, and information about these factors, had it been reported by Roayaie et al.[2], would have been of interest. These include details about the underlying fibrosis and extent of vascular invasion in the portal veins (Vp1-4) or the hepatic veins (Vv1-3),[9] which have been shown to be important predictors of outcome.[10,11] Currently, presence or absence and extent of vascular invasion and degree of fibrosis are the two main predictors of outcome of HCC. Large solitary tumors without vascular invasion are classified as UICC/AJCC stage 1, whereas tumors with vascular invasion single or multiple are classified as stage 2. Multiple tumors greater than 5 cm or tumors with Vp3 are classified as stage 3. These criteria best stratify HCC in the east and west as universal predictors of a single disease entity after resection and transplantation.[10,12] When looking beyond histopathologic parameters as we enter the arena of molecular and genomic medicine, we will have to find accurate molecular markers of outcome that will likewise stratify HCC prognosis. For example, recent work identified paraoxonase 1 as a serum biomarker for microvascular invasion in HCC using quantitative proteomic analysis.[13]

Preclinical studies suggest that novel prognostic markers and putative therapeutic targets can be found in the family of cell cycle regulators, including key compounds of iNOS cross-talk with IKK/NF-κB and RAS/ERK pathways (also targeted by sorafenib), the ERK inhibitor DUSP1, FOXM1 with its targets, and ubiquitin ligases.[14] Another promising marker, osteopontin, is an integrin-binding glycophosphoprotein that is expressed in transformed malignant epithelial cells and is believed to be involved in many physiologic cellular functions, such as regulation of migration, invasion, and metastasis of tumor cells as well as their survival. Elevated expression of osteopontin at the transcript (mRNA) level has been reported to be associated with the prognosis of patients with HCC.[15] Although these approaches are promising, further research in this field is necessary.

Roayaie et al.[2] provide an excellent paper that revisits many important issues pertaining to HCC prognostication and stratification of patients for surgical therapy. Our outcomes for patients with HCC involving the hepatic veins at the level of the confluence or the inferior vena cava have been poor, similar to what the authors report, and therefore we recommend resection only in selected cases (Vp1-3 with good performance status and early or no cirrhosis). Preoperative TACE should be considered in patients with ≥Vp3. Although the authors identify tumor size, alfa-fetoprotein level, and extent of vascular invasion as predictors for worse prognosis, in our view, they do not preclude selected patients from resection and might provide outcomes superior to best medical therapy.

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