

Anatomic versus nonanatomic resection in cirrhotic patients with early hepatocellular carcinoma

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Background. Whether anatomic resection (AR) for hepatocellular carcinoma (HCC) can really confer a survival advantage over non-AR (NAR), especially for cirrhotic patients, remains unclear.

Methods. Prospectively collected data of 543 cirrhotic patients in Child–Pugh class A submitted to AR (n = 228) versus NAR (n = 315) for early HCC in an Eastern (n = 269) and a Western (n = 274) surgical unit, were reviewed. To control for confounding variable distributions, a 1-to-1 propensity score match was applied to compare AR and NAR outcomes (n = 298).

Results. The 5-year recurrence-free and overall survivals of the 543 patients were 32.3% and 60.0%, respectively, without differences between the 2 centers (P = .635 and .479, respectively). AR conferred better overall and recurrence-free survival than NAR (P = .009 and .041, respectively), but NAR patients suffered from significantly worse hepatic dysfunction. After 1-to-1 match, AR (n = 149) and NAR (n = 149) patients had similar covariate distributions. In this matched sample, AR still conferred better recurrence-free survival over NAR (P = .044) but the beneficial effect of AR was limited to the reduction of early recurrence (<2 years) of poorly differentiated tumors and of tumors with microvascular invasion (P < .05), resulting in better overall survival (P = .018).

Conclusion. In cirrhotic patients, AR for early HCC can lead to a lower early recurrence rate in tumors with unfavorable tumor features, whereas NAR will not worsen the recurrence rate in well/moderately differentiated tumors or in the absence of microvascular invasion. (Surgery 2014;155:512-21.)

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HEPATOCELLULAR CARCINOMA (HCC) is 1 of the 5 most common malignancies worldwide and the third most common cause of cancer related mortality¹; although more common in East Asia, the incidence of HCC is increasing in the Western world.² Liver resection is widely accepted as a safe treatment with a low operative mortality as the result of advances in surgical techniques and perioperative management.^{3,4} Unfortunately, the high incidence of recurrence remains the major challenge in obtaining long-term results. Most recurrences occur in the liver as the consequence of subclinical metastases, originating from the primary tumor

growth through microscopic vascular invasion and peripheral spread, and are considered the most important factors associated with poor prognosis.^{4,6} On this basis, the systematic removal of a hepatic segment, confined by tumor-bearing portal tributaries, namely anatomic resection (AR), was suggested because it should be more effective for eradication of the intrahepatic metastases of HCC. On the contrary, most surgeons prefer to leave a greater portion of parenchyma of this functional unit, such as in non-AR (NAR), focusing on the preservation of a ≥ 1 -cm tumor-free margin to reduce postoperative liver failure in patients with cirrhosis.

It remains unclear whether AR can really confer a survival advantage over NAR. Some authors have described better long-term outcomes after AR compared with NAR, whereas others have not been able to demonstrate these benefits, as outlined by a recent meta-analysis.⁷ Discrepancies have probably to be considered a consequence of the intrinsic relatively low level of evidence of available literature represented by observational

Supported in part by a grant from Regione Emilia Romagna.
Accepted for publication October 8, 2013.

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0039-6060/\$ - see front matter

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<http://dx.doi.org/10.1016/j.surg.2013.10.009>

retrospective studies only. Meta-regression analysis on this topic suggested that both overall survival and disease-free survival after AR seem to be superior to NAR because the worse liver function reserve in the NAR group significantly affects prognosis.⁷ In particular, comparative data available from pertinent literature showed that patients submitted to NAR were characterized by a significantly higher prevalence of cirrhosis and more advanced hepatic dysfunction compared with patients in the AR group, and that such differences are able to modify postoperative results.⁷ Although a randomized, controlled trial (RCT) comparing operative approaches would be ideal, a retrospective analysis using a propensity score matching⁸ patients groups to reduce bias was used herein to better determine the impact of operative approach on recurrence-free and overall survival for cirrhotic patient with HCC undergoing resection.

METHODS

Patient selection was accomplished through 3 levels of inclusion criteria. First, all patients submitted to portosystemic shunts before or at the same time as hepatic resection, or treated as an emergency, or submitted to preoperative portal vein embolization were excluded from the analysis. Second, we considered eligible for the present study only those patients in whom no evidence of extrahepatic metastasis was present at the time of surgery, and at pathologic examination did not present tumor invasion into a major branch of the portal or hepatic veins, direct invasion of adjacent organs, or spread to the lymph nodes of the hepatic hilum. In addition, we retained only those cases in which a tumor-free margin of ≥ 1 cm was confirmed at pathologic examination; consequently, no tumor enucleations were included in the present study and all resections considered in the present analysis were curative resections at histology. Applying these criteria, between February 2001 and August 2010, 508 cirrhotic patients underwent a first curative resection at the Eastern Hepatobiliary Surgery Hospital of Shanghai, and between January 1997 and November 2011, 388 cirrhotic patients underwent the same procedure at the Department of Surgery and Transplantation of the University of Bologna: The policies of the 2 centers regarding indications for hepatic resection have been published elsewhere.^{4,9} Diagnosis of cirrhosis was confirmed on histologic specimens. To reduce potential confounding nomenclature of AR and NAR, a third level of inclusion criteria was adopted. Patients

with large tumors were excluded from the study that was limited to patients with a single nodule of HCC ≤ 5 cm or no more than 3 nodules none > 3 cm at histologic examination. In addition, the study was also limited to patients belonging to Child–Pugh class A. The final study population thus consisted of 543 cirrhotic patients, in Child–Pugh class A, resected for early HCC: A total of 269 patients came from the Eastern surgical center and 274 from the Western surgical center.

All patients underwent intraoperative hepatic ultrasonography and were deemed to have resectable tumors at the time of surgery. AR was defined as the complete removal of ≥ 1 Couinaud segment containing the tumor together with the related portal vein branch and the corresponding hepatic territory. The appropriate segment margins were identified with the discoloration of the parenchyma after ligation of the corresponding arterial and portal venous branches and with intraoperative ultrasonography assistance when necessary. NAR was defined as the resection of the tumor with a margin of ≥ 1 cm without regard to segmental, sectional, or lobar anatomy.

Pathologic and histologic evaluations of the resected specimens were carried out for all cases. The resected tumor, with its surrounding liver, was examined both microscopically and macroscopically for its histopathologic features. The maximal diameter of the tumor was taken as the tumor size. Curative resection was defined as complete macroscopic and microscopic removal of the tumor. Tumor differentiation and microscopic vascular invasion in the resected tumor were also determined.¹⁰⁻¹²

After discharge, all patients were observed periodically at follow-up to exclude possible recurrence of HCC: Biochemical liver function tests, serum alpha-fetoprotein level measurement and ultrasonography were performed 3 and 6 months after discharge and then according to an annual or semiannual surveillance program. When any recurrence was suspected, a computed tomography or magnetic resonance imaging was performed for confirmation. Recurrent lesions were managed aggressively by a multimodal approach, which included re-resection, transarterial chemoembolization, percutaneous radiofrequency ablation, and percutaneous ethanol injection. The treatment was decided by the pattern of recurrence, liver functional reserve, and the general condition of the patient at the time of recurrence. For selected patients with transplantable recurrence, salvage liver transplantation was also adopted. Since the end of 2008, Sorafenib (Nexavar; Bayer,

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