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Morphologic severity of cirrhosis determines the extent of liver resection in patients with hepatocellular carcinoma and Child-Pugh grade A cirrhosis

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ABSTRACT

Background: Liver resection is the mainstay of treatment for patients with hepatocellular carcinoma and compensated cirrhosis. We investigated the relationship between the morphologic severity of cirrhosis and post-hepatectomy liver failure (PHLF) and evaluated the role of cirrhosis staging in determination of the extent limit for liver resection.

Methods: The clinicopathologic data of 672 consecutive patients with Child–Pugh grade A liver function who underwent curative liver resection for hepatocellular carcinoma in Tongji Hospital from 2009 to 2013 were retrospectively reviewed. Severity of cirrhosis was staged morphologically and histologically. Risk factors for histologic cirrhosis and PHLF were analyzed. The extent limit of liver resection with reference to morphologic staging was studied.

Results: Morphologic and histologic stages were significantly correlated ($\tau = 0.809$, $P < 0.001$). Multivariate analysis showed that morphologic staging was the most crucial factor for histologic cirrhosis (odds ratio = 26.99, 95% confidence interval = 16.88–43.14, $P < 0.001$) and PHLF (odds ratio = 11.48, 95% confidence interval = 6.04–21.82, $P < 0.001$). The incidence of PHLF was high in patients with mild cirrhosis after resection of four or more liver segments (13.6%), those with moderate cirrhosis after major resection (38.1%), and those with severe cirrhosis or severe portal hypertension after resection of two or more liver segments (63.2% and 50.0%, respectively).

Conclusions: Morphologic severity of cirrhosis is an independent predictor of PHLF. Resection of fewer than four liver segments is justified in patients with mild cirrhosis. Major resection is not

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recommended in patients with moderate cirrhosis. In patients with severe cirrhosis or severe portal hypertension, only resection of fewer than two liver segments can be safely performed.

1. Introduction

Most hepatocellular carcinomas (HCCs) develop in cirrhotic livers, and 60%–90% of patients with HCC have underlying cirrhosis [1,2]. Liver resection remains a well-established therapy for HCC in patients with Child–Pugh grade A cirrhosis [3,4]. Post-hepatectomy liver failure (PHLF) reportedly affects 7.1%–50.0% of patients and remains a major cause of mortality among patients with concurrent HCC and cirrhosis [5–8]. High morbidity and mortality rates also contribute to poor long-term outcomes [9].

According to the European Association for the Study of the Liver and American Association for the Study of Liver Diseases guidelines for HCC with cirrhosis, liver resection should be restricted to patients with well-preserved liver function and without portal hypertension [10]. However, nearly half of patients with compensated cirrhosis without portal hypertension already have unequivocal histologic changes associated with cirrhosis, and the risk of liver resection may not be uniform [11]. Therefore, clinicians must remember that in addition to well-established parameters for evaluating liver function and portal hypertension, the severity of cirrhosis may also significantly affect the outcomes of liver resection in patients with compensated cirrhosis. Liver cirrhosis is associated with a poor prognosis in patients with HCC, but the severity of cirrhosis has never been used to evaluate the risk of liver resection. A staging system for compensated liver cirrhosis is needed to individualize liver resection and predict postoperative outcomes.

Although histologic examination remains the gold standard for evaluation of cirrhosis, it does not amount to much in preoperative decision-making. No reliable preoperative method with which to stage cirrhosis has yet been developed. In the past, we have met a lot of circumstances in which the morphologic changes of cirrhotic liver found during operation contravened the extent of liver cirrhosis evaluated by preoperative imaging tests; then, we had to change hepatectomy extent planning by reducing the extent of liver resection (ELR). Therefore, we started to pay attention to morphologic staging of the liver cirrhosis. We previously described a method of staging the morphologic severity of cirrhosis during laparotomy, which allows for quick judgment of the stage of cirrhosis before liver resection without the need to evaluate surgically resected specimens. However, the feasibility of this staging system for cirrhosis has neither been verified in large numbers of patients nor used to prevent PHLF or direct ELR.

In this study, the correlation between morphologic stage and histologic stage of cirrhosis was analyzed in patients with Child–Pugh grade A liver function who underwent curative resection for HCC. Furthermore, the ELR guided by morphologic staging was explored with reference to the incidence of PHLF and PHLF-related death. Finally, the correlations between severe portal hypertension (SPH) and severity of cirrhosis as well as the value of SPH in determination of the ELR were investigated.

2. Materials and methods

This study was approved by the medical ethics committee of Tongji Hospital, Huazhong University of Science and Technology, China. From January 2009 to December 2013, a consecutive series of 672 patients with Child–Pugh grade A liver function underwent curative resection for HCC in the Hepatic Surgery Center, Tongji Hospital. The potential for resection was preoperatively evaluated by ultrasonography, computed tomography, magnetic resonance imaging, and, in some patients, computed tomography volumetry. Liver function was assessed by a combination of the Child–Pugh classification, liver biochemistry, and indocyanine green testing. SPH was defined as the presence of esophageal varices on endoscopy with splenomegaly (a splenic thickness of >4.0 cm on transcutaneous ultrasonography) and a platelet count of $<100 \times 10^9$/l.

Morphologic staging of cirrhosis was based on the liver morphology observed intraoperatively as previously reported [12]: stage 1, mild cirrhosis (regenerated nodules $\leq$2 mm in diameter on the liver surface); stage 2, moderate cirrhosis (unevenly regenerated nodules $\leq$5 mm in diameter on the liver surface); and stage 3, severe cirrhosis (unevenly regenerated nodules $>$5 mm in diameter on the liver surface). The morphologic staging was performed by two surgeons who had participated in the operation. When the two surgeons disagreed, they discussed and reached a consensus on the morphologic cirrhosis score. In terms of the reproducibility of subclassifying cirrhosis, the kappa value was 0.813 for interobserver agreement using morphologic staging in our series, showing excellent agreement.

Intraoperative ultrasonography was routinely performed to identify the location of the tumor and determine the resection margin. The ELR was determined using Couinaud's definition of liver segments and the selection criteria for liver resection based mainly on an algorithm proposed by Makuuchi *et al.* [13]. Major resection was defined as resection of three or more liver segments, whereas minor resection was defined as resection of fewer than three segments. The definitions of the ELR are summarized in Table 1. Major resection was not performed in patients with morphologic stage 3 cirrhosis in our series because of the high incidence of PHLF. All tumors were completely resected with a tumor-free margin of $\geq$1 cm. The intermittent Pringle's maneuver was routinely performed to occlude the hepatic inflow during resection, and the inferior vena cava below the liver was simultaneously clamped when necessary.

Resected liver specimens were assessed by two pathologists blinded to the clinical data. The degree of histologic