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Surgical resection for hepatocellular carcinoma: moving from what can be done to what is worth to be done

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Abbreviations: HCC, hepatocellular carcinoma; CSPH, clinically-significant portal hypertension; MELD, Model for End-stage Liver Disease; NV, normal value

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Radical resection is the mainstay of treatment for organ tumors. The same could apply to hepatocellular carcinoma (HCC) if frequent multifocality and coexisting cirrhosis did not limit its role. Current guidelines (1,2) recommend resection only for single nodules *of any size* in patients without tumor-related symptoms and clinically-significant portal hypertension (CSPH) and with normal bilirubin (≤1 mg/dl). If this profile is not fulfilled, postoperative morbidity increases and long-term survival is significantly reduced. An extension of the recommendation has been repeatedly suggested, since in patients with CSPH (3,4), multiple nodules or intrahepatic vascular invasion resection can be attempted with high rates of technical success in experienced Centers, even though tumor elimination by surgery translates into an improved survival only in properly selected candidates. Actually, while tumor removal would be technically feasible in patients with a large tumor burden or impaired liver function, resection may be not worth attempting as survival could even be decreased.

In real life the decision to resect HCC is based on patient individual components and local conditions that are not captured by guidelines. Debate about resection is fuelled by several publications in which the outcome in suboptimal candidates is still felt acceptable, because it appears to be better than with other treatment options or no treatment. The controversy will further grow as improvement in surgical techniques and new drugs for hepatitis C virus will determine a reduction in postoperative morbidity, as it happened with hepatitis B virus. Finally, the growing epidemic of HCC in metabolic syndrome may also prime resections in large/multifocal tumors occurring in non-cirrhotic liver, although comorbidities and advanced age may preclude safe surgery in many of these patients.

In this issue of HEPATOLOGY, Roayaie *et al* (5) expose the surgical management of HCC within the Bridge database that collected information about new incident cases worldwide. In a cohort of 8,656 patients the Authors evaluated how frequently guidelines for resection

were followed and whether straying from them impacted on survival. A total of 862 (10%) patients were classified as ideal resection candidates and more than 80% of them underwent surgery; the remaining were mostly treated by ablation or embolization and experienced a two-fold increased mortality risk. These results could be used to support the superiority of resection, but they could also reflect the fact that associated conditions (advanced age, comorbidities) excluded those less healthy subjects from surgery. The main study interest is focused in the 7,794 (90%) patients who were classified as non-ideal candidates, 20% of whom were resected despite a suboptimal profile. Unfortunately, the database did not register intrahepatic tumor location and type of hepatectomy performed. As known, the propensity of hepatologists to refer and of surgeons to operate on non-ideal cirrhotic patients is influenced by the extent of planned resection and the perceived risk of the intervention. Therefore, the reader is left with the feeling that drivers of the decision to resect or not a non-ideal candidate were not thoroughly recorded and, consequently, non-ideal resected patients formed a not fully reproducible cohort. The fact that just few resected cases had severe liver disease (Child-Pugh C, bilirubin >2 mg/dl, severe portal hypertension reflected by platelets <50,000/mm^3) or very compromised general conditions (performance status 3-4) suggests that clinicians took into account liver function, tumor location and general health status when favoring resection. Indeed, the <5% postoperative mortality rate indicates a quite appropriate evaluation of short-term surgical risks. However, while remaining acceptable, in non-ideal patients the risk of 90-day perioperative death was almost four times higher than in ideal ones (4.5% *vs* 1.2%), and the fact that resection can be performed without excessive early mortality should not be understood as if the long-term survival would be as good as in optimal candidates.

The analysis in all resected patients (ideal and non-ideal) showed that CSPH and bilirubin >1 mg/dl were not associated with mortality if taken separately, while their association

conditioned a worse prognosis. Multivariate analyses were performed using both a more sensitive (platelets <100,000/mm^3 *or* evidence of varices/splenomegaly) and a more accurate definition of CSPH (platelets <100,000/mm^3 *and* evidence of varices/splenomegaly). Even though not significant in both models, CSPH was shown to increase the hazard ratio (from 1.17 to 1.24) with a trend toward significance (p from 0.12 to 0.08) moving from the first to the second analysis. Instead, multivariate models in non-ideal candidates (resected and non-resected) exposed CSPH as a negative prognostic factor, stressing once more the significant impact of CSPH on prognosis in cirrhotic patients.

Certainly, different methods of defining CSPH (hepatic vein pressure gradient *vs* surrogate markers) and different study designs fuel the debate about the role of CSPH. A Japanese study (6) confirmed the impact of portal hypertension on long-term outcome after resection, while Italian studies reporting their data (3) or using propensity-score matching (4) suggested a lack of impact. Single center data should be carefully assessed in order to ensure that postoperative mortality and survival rates reflect the figures observed in referral centers. In addition, propensity score studies need to be validated to avoid the flaw due to the exclusion of outliers that are indeed detected by the assessment of the key parameter, which in liver resection may be portal hypertension. This relevant role of CSPH is reinforced by a recent Barcelona (7) and two Asian meta-analyses (8,9).

Interestingly, the study by Roayaie *et al* raises the value of bilirubin >1 mg/dl for a better stratification of the patients classified as having CSPH using suboptimal definitions in comparison with hepatic vein catheterization. Bilirubin role was identified in the seminal study in Barcelona and is included in guidelines. Such ‘breakpoint’ is frequently dismissed, yet it appears to sense the surgical risk of non-ideal candidates as per CSPH while serving

to predict the survival of resected patients. Bilirubin is also a covariate of the Model for End-stage Liver Disease (MELD) score, which is a reliable predictor of postoperative liver failure if higher than 10 (4).

Roayaie *et al* report a 15% mortality risk reduction in ablated patients as compared to resected ones, thus endorsing the recommendation to give priority to ablation in patients with small tumors that can be effectively and safely ablated. As expected, non-ideal patients who were transplanted had the best outcome. This reinforces the role of transplantation in guidelines: first-line treatment for non-ideal resection candidates fulfilling criteria for transplant. Long-term survival was better with resection than with transarterial therapies, but as mentioned before, it is impossible to ascertain whether the driver for an improved outcome was surgery by itself or the bias introduced by clinical decisions and/or available expertise in non-surgical options.

After all, Roayaie's paper basically argues on how guidelines should be used in an individual patient who could undergo different treatments, and whether the principle should be endorsed that all 'curative' options must be explored before relying on 'palliative' ones. This suggestion tends to privilege initial activity (initial cure with risk of recurrence) rather than long-term survival which is the real goal. We believe that guidelines constitute a useful framework in which clinicians' decisions can be tested, especially for patients with a well-defined profile. They help protecting from overtly incorrect choices, safeguarding health system quality. Instead, patients with characteristics that are not within the strict recommendation require the assessment by experts, who may make non-ideal decisions on non-ideal patients but always consider individual and general factors favoring either one of the available treatments (Table 1). In such perspective, guidelines are like the fundamental rules for playing a sport, whose ignorance does not allow admission to

practice. However, as in professional sports where the bare application of fundamentals does not forcibly imply to win the game, the too rigid interpretation of guidelines could stop experimenting new potentially successful strategies and possibly preclude some patients from benefiting from more effective treatments chosen on expert judgment. Thereby, guidelines expose the current recommended practice and data such as those provided by Roayaie *et al* may open the door to prospective and robust investigations in the area of surgical resection. These may result in data leading to modify the current guidelines or just reinforce them. In the absence of such clarifying information, the debate will continue.

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Table 1. Factors concurring to select treatment for hepatocellular carcinoma confined to the liver.

Drivers of Treatment Selection	In favor of RESECTION	In favor of TRANSPLANTATION	In favor of ABLATION	In favor of TRANSARTERIAL THERAPIES
Patient				
▪ Age	≤ 75 years	≤ 70 years	no limit	no limit
▪ Performance Status	0	any grade (high MELD)	0	0
▪ Comorbidities	absent / minor	absent	major	major
Tumor				
▪ Size	≥ 3 cm	single ≤ 5 cm	≤ 3 cm	any size
▪ Number	single	up to 3 nodules ≤ 3 cm	up to 3 nodules	large / multinodular
▪ Location within liver	peripheral / exophytic growth	any site	central, far from vessels, bile tract and viscera	central
▪ Vascular invasion (branch / segment)	not relevant by some	absent	absent	not relevant by some
▪ Satellites	not relevant only in anatomic resections	not counted when < 1 cm	absent	not relevant
▪ Alpha-fetoprotein	the lower the better	< 1,000 ng/ml	any level	any level
▪ Perceived anti-tumor efficacy	high	very high	high	moderate
Liver Disease				
▪ Quality of parenchyma	non-cirrhotic	cirrhotic	cirrhotic	cirrhotic
▪ Portal hypertension	absent / mild	any degree	any degree	any degree
▪ Bilirubin (NV ≤ 1 mg/dl)	normal	any level	normal / ≤ 2 x NV	normal / ≤ 2 x NV
▪ MELD score	very low	any value	low	low
Local Factors				
▪ Specialized surgical expertise	available	available	not available	not available
▪ Interventional non-surgical expertise	not available	not relevant	available	available
▪ Organ donation rate	low	high	low	low
▪ Competition with non-HCC patients on transplant waiting-list	high	low	high	high

Abbreviations: MELD, Model for End-stage Liver Disease; NV, normal value; HCC, hepatocellular carcinoma