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Editorial

Outcomes of resection surgery for hepatocellular carcinoma: Does size matter?

Hepatocellular carcinoma (HCC) is one of the major public health threats in the world. It accounted for 745,500 deaths worldwide in 2012, which was the second and 6th leading causes of cancer mortality in males and females, respectively.[1] Liver transplantation, surgical resection, and local ablation therapy are recommended as the curative treatment modalities for patients with early-stage HCC.[2] However, the application of liver transplantation is often limited in clinical practice due to the scarcity of liver transplantation donors. Hence, surgical resection and local ablation therapy are performed in most patients with small HCC and with a well-preserved liver function. Several studies have been conducted to compare the treatment efficacy and long-term prognoses between resection and ablation in the recent years.[3,4] Most of the studies disclosed that HCC patients who underwent resection surgery had a significantly lower recurrence rate than those who received local ablation therapy. Moreover, with the advances in surgical technique, as well as peri-operative care, several studies demonstrate that surgical resection could provide a long-term survival benefit for patients with non-early stage HCC and even in the setting of vascular invasion or extra-hepatic metastasis.[5] Consequently, surgical resection remains the firs-line curative therapeutic strategy for HCC if the patients are not contra-indicated for operation.

Nevertheless, recurrence after surgical resection for HCC is common, which may in turns lead to early mortality.[6] Factors determining the recurrence of HCC after resection include host factors (such as age, gender, genetic factors, and performance status), tumor factors (including tumor burden, serum alpha-fetoprotein levels, surgical cut margin, the presence of vascular invasion or extra-hepatic metastasis, and tumor cell differentiation), and field factors in the background liver (such as the grade of inflammation, the stage of fibrosis, steatosis, liver functional reserve, portal hypertension, ongoing viral replications and mutations, etc).[7–9]

Among them, vascular invasion is a major determining factor for tumor recurrence after resection. Moreover, previous studies also demonstrated that HCC patients who had microvascular invasion and underwent surgical resection had a higher rate of developing recurrence beyond the Milan criteria, which made salvage liver transplantation infeasible at the time of recurrence.[10] It indicated that vascular invasion presented an aggressive tumor biology. However, it is difficult to detect the vascular invasion, especially microvascular invasion, before operation. To more accurately select the treatment modality and to predict the prognosis, it is crucial to search for a clinically applicable surrogate for vascular invasion when HCC is diagnosed.

Previous studies confirmed that larger tumor size had a higher incidence of vascular invasion and satellite nodules compared to smaller tumor.[11] However, the cut-off value of the tumor size to determine post-operative recurrence is not fully elucidated. In this issue of the *Journal of Chinese Medical Association*, Tsai and his colleagues investigated the prognostic factors for patients with HCC and underwent surgical resection.[12] They disclosed that HCC patients who had a tumor size 5 cm or larger had a significantly lower overall survival rate and higher recurrence rate than their counterpart. The cumulative mortality rates at 5 years after surgical resection were 13.2% and 43.3% for patients with a tumor size <5 cm versus 5 cm or larger, respectively ($p < 0.0001$). And it was further confirmed after adjusting for the potential confounding factors by a multivariate analysis and considering the competing risk event of death. It indicated that a tumor size of ≥5 cm could be served as an important prognostic factor for HCC patients who underwent surgical resection. Therefore, patients who had a large HCC should be followed-up with a more frequent surveillance interval or received adjuvant therapy after the operation.

Most of the patients (84.5%) enrolled into this study had a single tumor. Whether single large (>5 cm) HCC (SLHCC) should be classified as Barcelona Clinic Liver Cancer (BCLC) stage A (early stage) or B (intermediate stage) is still under active debate.[13] From the data of this study, it implied that patients with SLHCC might not be suitable to be designed as BCLC stage A due to a significantly poorer prognosis than those with a small tumor. Nevertheless, although patients with SLHCC had a lower overall survival rates after resection than those with early stage HCC. Their long-term outcomes are still better than patients with SLHCC and underwent transarterial chemoembolization, which is considered as the standard of care for BCLC stage B HCC.[13] Consequently, surgical resection could be the first-line treatment modality for SLHCC. And SLHCC might be an independent and intermediate stage between BCLC stage A and B, although more prospective studies are needed to validate this concept.

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Nevertheless, several important issues need be concerned for this paper. First, in this study, a total of 17 (around 4%) patients dead within 60 days after resection, in which the early mortality rate seems to be higher than that reported by the previous studies.[14] And the patients with early mortality and early recurrence were excluded from the final analysis. It may underestimate the recurrence rate and confound the analysis of factors that determine the prognosis. Second, several important prognostic factors, such as vascular invasion, viral factors (hepatitis B virus or hepatic C virus genotypes, viral load, mutations, and antiviral therapy), the grade of hepatic inflammation and steatosis, the degree of portal hypertension were not addressed in this study.[15] Further more comprehensive studies are warranted to elucidate this issue. Third, the median follow-up period of this study was relatively short (22 months) and most of the patients had early HCC recurrence with 2 years after resection. It is difficult to search for the prognostic factors that determine the late recurrence in this cohort study.[8]

In conclusion, for patients with HCC and underwent surgical resection, a tumor size 5 cm or larger was associated with a poorer overall survival rate and a higher early recurrence than those with a smaller tumor. They should be followed up with caution and the surveillance interval for recurrence after the operation might need to be shortened.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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