



## Anatomic Versus Non Anatomic Surgical Resection in Patients with HCC on Cirrhosis a Surgical Dilemma

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### Editorial

Hepatocellular (HCC) is 1 of the 5 most common malignancies worldwide and the third most common cause of cancer related mortality with 500,000 deaths globally every year. Hepatic resection is the first-line therapeutic option and it is accepted as a safe treatment with a proven impact on prognosis, with a low operative mortality as the result of advances in surgical techniques and perioperative management [1]. These advances improved the outcomes of hepatic resection for HCC with low operative morbidity and mortality otherwise surgical resection is applicable in only about 20% to 30% of patients with HCC, since most have poor hepatic reserve function caused by underlying chronic liver disease and multifocal HCC [2]. Although hepatic resection is one of the curative treatments for hepatocellular carcinoma, the recurrence rate of HCC even after curative resection is quite high, estimated to be approximately 50% during the first 3 years and more than 70% during the first 5 years after curative resection and so the postoperative long term results remain unsatisfactory [3,4]. The reasons for the poor prognosis was supposedly due to the high incidence of intrahepatic metastasis and high incidence of multicentric occurrence of *de novo* HCC based on the precancerous status of the remnant diseased liver [5]. With respect to intra-hepatic recurrence, macro-portal invasion and intra-hepatic metastasis were considered to be the most strongly risk factors affecting the postoperative prognosis. However, the importance of each recurrence pattern has not been clarified yet. Previously, portal vein dissemination was considered to be the main route for intrahepatic metastasis and intra-hepatic metastasis *via* vascular invasion was thought to be a key factor of recurrence. This led to the notion that anatomical resection, determined by the portal venous flow area, may prevent intrahepatic metastasis of HCC [6-8]. On this basis, Anatomic Resection (AR), which was described by Makuuchi et al. [9], is the systematic removal of a hepatic segment confined by tumor-bearing portal tributaries. Theoretically, this procedure may be effective in eradicating intrahepatic metastasis of HCC, leading to more favorable results in HCC patients. Based on the portal blood flow dissemination theory, some authors have used AR for HCC, and demonstrated oncological and survival benefits of AR compared with Non-Anatomical Resection (NAR) for HCC [10,11]. However, the comparisons of the outcomes between the anatomical hepatic resection and partial or nonanatomical or limited hepatic resection have been argued without any clear conclusion. Some authors have reported that AR may prevent hepatic recurrence and prolong survival. In their systematic review of 18 observational studies involving 9036 patients, Cucchetti et al. [12] suggested that AR provided better 5-year Overall Survival (OS) and Disease-Free Survival (DFS) than did NR. In other meta-analyses, Zhou et al. [13] also reported that AR significantly provided a better 5-year OS than did NR. The rationale for this improved prognosis with AR is based on the high rate of intrahepatic metastasis caused by the spread of HCC cells through the portal vein; AR theoretically reduces the risks for local and intrahepatic recurrence compared with NR. Moreover in a large research based on a Japanese national data analysis, Eguchi et al. [7] illustrated that the RFS rate in AR was superior to that in NAR, but significant statistical difference was not observed in patients with HCC more than 5 cm. However, AR can be more difficult to perform and carries more risk than NR for patients with low liver function (e.g., those with cirrhosis). In general, more liver parenchyma is resected in AR than in NR, which carries a high risk of increased intraoperative blood loss and longer surgical time. So surgeons always tend to choose AR in HCC patients with good liver function, small tumors, and no cirrhosis in clinical practice. According to more recently established concepts, based on the evidence of HCC recurrence occurring even in cases treated by hepatic resection and liver transplantation for HCC, intrahepatic metastasis occurs according to the Tumor Blood Flow (TBF) or systemic rehoming to the remnant liver [14]. Sakon et al. [15] defined the patterns of intrahepatic recurrence of HCC as follows: (1) local IM: HCC recurrence around the tumor by direct spread of the tumor through the portal blood flow or venous drainage; (2) systemic IM: HCC recurrence caused by circulating tumor cells (CTCs); (3) MC: multicentric HCC

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recurrence caused by *de novo* development of HCC. HCC circulating tumor cells have been detected in 81% to 88% of patients at the time of surgery [16]. Early circulating tumor cells are thought to be spread by branches of the portal vein and AR aims to resect the liver perfused by the supplying portal vein based on Couinaud's segments. Thus theoretically, AR should resect Micro Metastases (MMTs) within the anatomical segment and thus reduce the risk of recurrence. Thus, it is reasonable to postulate that AR would be more beneficial than NAR for the clearance of MMTs and circulating tumor cells, thus decreasing the Local Recurrence (LR) caused by "nearby" MMTs, but not Distant Recurrence (DR). Considering these points of view has been taken in account conventional limited resection, Non Anatomic Resection (NAR) as potential surgical treatment of HCC. It is focused on achieving a non-tumoural liver parenchyma rim, without consideration of the Glisson's pedicles. Because of the underlying cirrhosis, NAR is regarded to be useful for retaining as much liver parenchyma as possible [17]. Due to the unbalance between AR and NAR, it was difficult to reach a consensus about the advantage of AR in previous studies. Based on this concepts others Authors have failed to detect survival benefits of AR [18,19]. Okamura et al. and Marubishi et al. [20,21] questioned the advantage of AR and showed the incidence of HCC recurrence were similar between the AR and NAR groups in the recent researches. Thus, the superiority of AR compared to Non Anatomic Resection (NAR) remains controversial. Therefore, surgeons have to maintain a balance between radical surgery and function of the remnant liver, which is the focus of the dispute between AR and NAR. No advantages are clear neither in terms of overall survival: the 5-years overall survival rate is 64.9% for AR and 61.1% for PSR. To date, there has been no randomized controlled study to compare outcomes between these two resection methods and the main problem that surgeons face while operating on patients with cirrhosis is the balance between achieving a radical intervention while simultaneously preventing the development of postoperative liver failure that could ensue from removal of too much liver parenchyma. This problem is the basis of the challenge on which technique is more effective: AR, which should theoretically be a more radical procedure from an oncologic point of view, or NAR, which should reduce the risk of postoperative hepatic failure.

## Conclusion

The oncological advantage of AR has been actively studied and discussed for decades. However, the available data remain insufficient to prove the prognostic advantage of AR due to the following reasons: first, the definition and surgical technique of AR are not standardized among institutions. Second, because the baseline characteristics vary considerably among previous studies, it was difficult to determine the pure prognostic advantage of AR, even by meta-analyses, due to the heterogeneity of the target population. Third, because of the significant differences in the underlying liver function between the populations treated by AR and non-AR, a simple prognostic comparison would not be free from selection bias. A randomized clinical trial could be the answer to this dilemma.

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