



Impact of anatomical resection for hepatocellular carcinoma with microportal invasion (vp1)

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Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide (1), with an upward trend in most countries over the last 20 years. While surgical resection remains as the first-line therapy for HCC, the relevant high postoperative recurrence rate is still the major concern, responding for poor survival in most cases (2). The comparison between anatomic resection (AR) and non-anatomic partial resection (NAR) has been discussed for several decades, making it more clear of their application based on tumor features and underlying liver disease, but yet much needs to be completed.

Makuuchi (3) first proposed AR in 1985, namely systemic resection of the segment which the tumor locates in, to theoretically remove microportal invasion (vp1), the tumor cells spreading along microportal vessels. After that, quite a few studies followed to explore the potential benefit of AR for HCC patients. AR was expected to positively affect the prognosis by eradicating the potential tumor-bearing portal territory, while the main merit of NAR was to retain more liver parenchyma in order to prevent liver failure. Tomimaru *et al.* (4) and Hirokawa *et al.* (5) argued that AR was not able to provide better DFS or OS, and the latter even reported worse short-term outcomes following AR such as implications and longer hospital stay. More studies (2,6-8), however, tended to come up with opposite conclusions that patients achieved better survival after an AR, mainly DFS, and our previous meta-analysis (9), enrolled 25 studies including 10,216 patients, echoed their findings.

No prospective randomized controlled trial (RCT) was available until 2017, when Feng *et al.* (8) reported their

double blinded research exploring potential influence of the two surgical procedures on prognosis of HCC patients. In this RCT, AR resulted in decreased 2-year local recurrence and later recurrence in comparison with NAR, but in terms of distant recurrence or overall recurrence, neither operation procedure was superior. The different effect of the operation approaches (AR *vs.* NAR) on the two patterns of recurrence may be explained by the corresponding recurrent mechanism. While multicenter tumors account for most recurrences in long term postoperative period, intrahepatic metastasis is accepted as the major cause of early recurrence (<2 years) (4) which often occurs in the same sector of the primary tumor. Therefore, early local recurrence could be prevented as AR eradicated vp1 that have extended away from the primary tumor. Micro-metastases through portal vein system are frequently found in soon recurrent cases after resection, and were reported to be able to spread as far as 6.1 cm from the original tumor (10), which is generally not removable by local resection. Apart from spreading along the portal vein flow, however, tumor cells can also invade proximally and distally through various of processes which result in adjacent segment invasion or even metastasis far away from the primary mass (10), meanwhile making it more difficult to distinguish intrahepatic metastases and multicentric carcinogenesis. This may partially explain why some researches (4,10) fail to indicate the superiority of AR for reducing recurrence as AR is not able to control multicenter carcinogenesis or intrahepatic metastasis evolving other segment from the primary tumor.

It's worthy to mention that early stage HCC (small

solitary without macroscopic invasion) is more frequently detected with the increasing aware of physical examination of public and the modern screening technology. However, even small single HCC were found with a range of 23.0–57.1% (2,5,7) of vp1 in reports, and/or moderately/poorly differentiated. In the retrospective study, Hirokawa *et al.* (5) reported the similarity between AR and NAR for surgical outcomes of small solitary HCC, and they also reported prevention advantage of NAR in regard to bile leakage and abdominal abscess. In the other hand, by conducting a nationwide investigation including 5,781 patients, Eguchi *et al.* (11) demonstrated AR was superior for single HCC with the size between 2 and 5 cm for its ability to improve DFS without worsening perioperative morbidity or mortality, especially for those poorly differentiated. And patients assigned to each group had equal liver function, revealing the better outcome in AR group was not a consequence of better liver function. AR was not necessary for tumor less than 2 cm as these tumors can be effectively treated by other approaches like radio frequency ablation, while oncologic behavior was so dominant when tumor grow larger than 5 cm that AR was not able to improve the prognosis. Interestingly, patients with small solitary HCC accepted NAR without local recurrence had similar survival with that of the whole AR group (7) in another study, indicating that AR could improve prognosis by controlling regional tumor relapse. Thus, patients with small solitary HCC, especially with the size 2–5 cm and preserved liver function, are expected to benefit from an AR, while NAR is valid for cirrhotic individuals with comparable surgical outcomes.

It is a well-established fact that microvascular invasion (MVI), mostly vp1, adversely influence disease-free survival (DFS) (4,10,12). Micro-metastases occur when malignancy cells spread along with the portal vein which are evolved with HCC, and this hypothesis was also supported by the recent RCT (8). However, evidences are hardly available comparing the effect of AR *vs.* NAR with special attention to vp1, due to its identification depending on surgical specimen. To our knowledge, the study by Shirabe *et al.* (13) was the first to demonstrated that AR contributed to a superior DFS rate in HCC patients with vp1, though this advantage of AR was not found when invasions evolved more than one portal vein branch which was probably due to the very limited number of this group (N=11). Five years later, AR was proved to lead an encouraging result in patients with MVI or poorly differentiated but early HCC (2), while there was no difference between

AR and NAR when MVI was absent. Similar results were identified in another two studies (6,12) that particularly focused on HCC with vp1. However, Famularo *et al.* (14) found that AR could not provide promoted DFS, early or long term, even for HCC with MVI, but sample size of HCC with MVI was very limited, with 30 and 38 assigned to AR and NAR, respectively, which might partially contributed to the insignificant result. In a view enrolling 546 patients with vp1 (1), NAR was not suppressed by AR in terms of 5 years OS or DFS. In addition, NAR group even resulted in comparable recurrence rate with that of hemi-hepatectomy, the details of tumor feature in these subgroups, however, were not precisely reported. In the other hand, this retrospective study indicated superiority of AR of controlling local recurrence when compared to NAR. In a whole, given its clearance of potential intrahepatic metastases via portal system, it seemed most researches have reached a consensus that an AR is superior for local recurrence control, especially for HCC with high risk of vp1, otherwise a NAR is an alternative option to guarantee safety.

MVI/vp1 is now commonly identified as a risk factor for poor prognosis, but unlike macroscopic invasion, it's generally not preoperatively detectable. Since AR and NAR are expected to lead different outcomes according to the presence of MVI, it's a great challenge to decide the operation procedure as MVI can only identified with surgical specimens. AFP, the well-known diagnosing variable for HCC, has long been regarded as a strong predictor (when >100 µg/L) for MVI (6), regardless of tumor size and number. Furthermore, AFP, as well as tumor size/number/volume, was used to build a new artificial neural network (ANN) (15) which was also able to predict the tumor grade. Consequently, ANN was found more reliable with a higher accuracy (91% *vs.* 85%) for predicting MVI than that of conventional logistic regression model. From our experience, however, the use of ANN for predicting tumor grade and the presence of MVI is limited possibly because of its relevant complexity, while AFP is much easier accepted for its wide application in routine clinical use.

To sum up, an AR is expected to lead to superior early surgical outcomes (<2 years), mainly DFS, for HCC patients given its potential ability to control vp1. Its effect on long-term outcomes, however, remains controversial. An AR is recommended for patients with high risk of vp1 or poorly differentiated when feasible, while a NAR should be conducted with hepatic dysfunction or negative AFP. Yet more well designed with large sample research and

RCT need to be done to confirm the influence of operative procedures, especially long-term outcomes, in patients with different tumor features and underlying disease.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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