



# Anatomical or non-anatomical resections for hepatocellular carcinoma: a never-ending debate

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Hepatocellular carcinoma (HCC) is the most frequent primary tumor of the liver and the sixth most common cancer worldwide with more than 800,000 cases per year (1). Potentially curative treatments such as liver transplantation (LT), liver resection (LR), and ablation (in selected cases) currently represent the best available options to offer long-term survival to patients (2). Given the worldwide scarcity of organs for transplantation, hepatic resection (open or minimally invasive), is frequently considered as the first option upon presentation. One of the most intriguing and longstanding debated issues among the hepatobiliary surgical community is the type of surgical resection that should be performed. Should we systematically pursue an anatomical resection (AR) or non-anatomical resection (NAR) for HCC?

Despite a low probability of lymphatic spread, HCC is associated with a high rate of capsular invasion, vascular invasion, and intrahepatic metastasis in the form of satellite nodules (3). It has been previously theorized and shown in preclinical studies, that the cytoarchitecture of this tumor differs from other primary or secondary cancers. Indeed, a small artery represents the feeding vessel while the portal stream is responsible for the drainage. Artero-portal shunts within the tumor allow for cancer cells to spread intrahepatically, eventually leading to metastasis

within the same anatomical area of the liver (4). Based on these studies, Makuuchi *et al.* theorized that LRs for HCC should be anatomical, removing the whole tumor-bearing area vascularized by the serving portal pedicle, to avoid residual satellite nodules around the tumor's area (5,6). Despite many retrospective studies reporting an association between ARs and improved oncological outcomes, level A evidence is lacking (7,8). The only randomized controlled trials to date have been reported by Shi *et al.* and Feng *et al.* (9,10). Unfortunately, Shi *et al.* reported an improvement in oncological outcomes when a >2 cm margin is pursued during resections, answering the question of the length of margins rather than on ARs. On the contrary, Feng *et al.* were the first and only to report a randomized controlled trial on AR *vs.* NAR, focusing on 2 years recurrence-free survival as a primary endpoint (10). No differences were found between the groups, neither in postoperative outcomes nor in the oncological outcomes, including overall survival and recurrence-free survival. However, AR showed a significantly better local recurrence-free survival (P=0.01) and a lower number of local recurrences within 2 years (30% *vs.* 59%; P=0.001). This trial is very important for several reasons. First and foremost, it shows that when we, as surgeons, struggle to perform ARs for HCC believing that we might change the long-term outcome of our patient, we

are in fact only gaining local control of the disease within the first 2 years after surgery. Survival of patients will not be affected by our surgical effort until proven otherwise. Second, it highlights that the outcomes on which we should design our studies on surgical resection for HCC should be well-pondered. Indeed, as shown in many studies, HCC recurrences have different timing (early, late) and patterns (intrahepatic local, intrahepatic diffuse, *de novo*, true, extrahepatic), and our surgical effort will probably impact few, if any, of these rather than recurrences overall (3,11,12). Finally, what is the most important outcome measure in oncological trials? What do patients ask clinicians when they know they should be operated on for cancer? “Doctor, will I die from this?”, “Will I see my kids grow up?”. Overall survival is the outcome and that should be the endpoint that we are most interested in. Feng *et al.*, in their randomized controlled trial, showed that whether you perform an AR or NAR, this will not impact the life expectancy of our patients. In this issue of the *HepatoBiliary Surgery and Nutrition* journal, Lee *et al.* confirm this in a nice study on patients affected by HCC in the posterosuperior segments, operated on by laparoscopic approach. Using a propensity score matching, they compared laparoscopic AR (LAR) *vs.* NAR (13). They found that NAR was better than LAR in terms of short-term outcomes (blood loss, operation time, and length of hospital stay). Most importantly, they showed that AR was associated with lower rates of intrahepatic recurrence but that the overall survival was similar between the two groups. Again, this echoes the concept that the effort of pursuing AR might reduce the number of intrahepatic recurrences but eventually, will not change the long-term survival of patients. The authors give a further explanation of this result performing a subgroup analysis on the type of treatments that could be offered to recurrent tumors. Five (35.7%) patients in the NAR group were treated with potentially curative options while in the AR no patients underwent re-resection. This means that despite you recur more if you perform an NAR initially, you can be more often salvaged. Indeed, AR frequently implies a greater parenchymal sacrifice, as also demonstrated by the number of major hepatectomies and bisegmentectomies in the study by Lee *et al.* In this setting, a potential benefit might be seen in case the concept of AR is paired with the one of parenchymal sparing resections (14,15).

LRs in the posterosuperior segments are challenging, especially in cirrhotic patients (15,16). ARs in such challenging cases could lead to longer operative times, higher blood loss, longer hospital stays, and eventually more

postoperative complications as compared to NAR. Therefore, one should consider that for a peripheral lesion in a posterosuperior segment, performing an AR might translate into worse postoperative outcomes without affecting survivals. Of course, this is not clear-cut. Indeed, patients with HCC represent a heterogeneous group of individuals presenting with different performance status, burden of disease, and degrees of liver function, who consequently have different treatment alternatives and salvage options in case of recurrence. For patients with HCC arising from cirrhosis, with impaired liver function that can be eventually salvaged with LT in case of recurrence, pursuing an AR increasing the possibility of postoperative complications and decompensation, without impacting the long-term survival, might not be the best choice. On the other hand, in the case of an HCC on a healthy liver or non-transplantable patient, surgical resection might be the only potentially curative alternative, and pursuing an AR might be a reasonable approach to minimize the possibility of recurrence. Finally, a technical consideration should also be made. When choosing between AR and NAR, the lesion’s position plays a role as sometimes AR is the inevitable option (large lesions, deeply located, close to major structures), while in some others NAR might represent the most convenient choice (peripherally located, small lesions).

In conclusion, the debate on AR *vs.* NAR is not yet concluded. Current evidence suggests an advantage in terms of early local recurrences for ARs, which, however, does not translate into a survival benefit. Nowadays, the choice to perform an AR or NAR should consider the presentation of the patient, the liver function, the disease burden and location, and the potential alternatives in the case of recurrence, aiming to decrease the chance of postoperative complications and ensure long-term survivals.

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