Review

Are Tumor Exposure and Anatomical Resection Antithetical during Surgery for Hepatocellular Carcinoma? A Critical Review

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Key Words

Cirrhosis · Hepatectomy · Hepatocellular Carcinoma · Intraoperative Ultrasound · Liver

Abstract

Hepatic resection is the most potentially curative local therapy for patients with hepatocellular carcinoma (HCC). However, the high rate of postoperative recurrence, 50–70% at 3 years, remains a major concern. Such recurrences usually occur in the liver owing to the high propensity of HCC to invade the portal vein branches and the underlying liver cirrhosis, which is the ideal background for HCC development. Two pivotal surgical techniques are commonly used to reduce such recurrences: anatomical resection (AR) and achievement of negative margins. However, controversies exist about the definition of anatomical resection and the requisite width of negative margins. Consequently, a consensus on these issues is far from being achieved in the specialized surgical community. Review of the literature and author's discernment support AR for HCC larger than 2cm, and tumor exposure when the tumor is in contact with major vessels. Therefore, tumor exposure is not a contradiction to an AR properly carried out.

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Introduction

Hepatocellular carcinoma (HCC) is one of the five most common malignancies worldwide, and its incidence is increasing in many countries [1]. Apart from liver transplantation, hepatic resection is the most potentially curative locoregional treatment for HCC. Improvements in perioperative care and refinements in surgical techniques have significantly increased the safety and survival rates of hepatic resection in the last few decades [2, 3]. However, the high rate of postoperative recurrence, 50–70% at 3 years, remains a major concern [4, 5]. Such recurrences usually occur in the liver owing to the high propensity of HCC to invade portal vein branches [6], and to the underlying liver cirrhosis, which is the ideal background for the development of HCC. Two pivotal surgical techniques are usually recommended to reduce postoperative recurrence: anatomical resection (AR)[7], and achievement of negative margins [8,9]. However, in the surgical community, some confusion still exists about these issues, particularly, about their definitions and for the rules governing their practical application. Therefore, this study aimed to review these two techniques of hepatic resection for HCC.

Anatomical Resection (AR)

AR is usually recommended because the removal of the portal vascular bed containing a tumor is theoretically expected to be effective from an oncological perspective. The rationale for this is that removal of the vascular bed will ensure the removal of any potential satellite tumors in the liver, which may have risen because of the tumor's tendency to invade the portal veins [6]. To achieve an optimal compromise between the need for the complete removal of the area occupied by the tumor and the need to spare the liver parenchyma, Makuuchi et al. proposed systematic subsegmentectomy in 1985 [7], and successfully applied it, mainly in Japan, with excellent results [10]. Given the technical skill demanded by this procedure, which involves free-hand ultrasound-guided puncture of thin portal branches, an alternative method of segmental or subsegmental AR has recently been introduced: the ultrasound-guided finger compression technique [11]. Any other technique that does not aim to precisely identify the afferent portal pedicle and the segmental or subsegmental territory it supplies should be considered a non-anatomical resection (NAR), regardless of whether it is associated with minor or major parenchymal removal. This is a crucial point that should be considered when comparing different studies on segmental or subsegmental AR and NAR for HCC. When the surgical technique is not detailed, the results may be biased by significant conceptual and technical issues, which make the conclusions invalid.

As a partial consequence of this inadequate comparison, it remains unclear whether hepatectomy performed in clinical practice should involve AR or NAR. No prospective randomized trials have been available to date, and two meta-analyses on the topic have reported conflicting findings [12, 13]. Moreover, a recent meta-regression analysis showed that even after adjusting for some important covariates, the available studies on AR and NAR could not be easily compared [14]. A review of the most relevant studies published on this topic in the last decade is presented in table 1 [10,15–20]. Most of the studies report a trend of better 5-year overall survival in the AR group than in the NAR group; in particular, it seems that the anatomical approach is advantageous mainly for lesions measuring >2 cm and <5 cm [17, 18, 20]. However, because comparisons of AR and NAR remain biased owing to technical issues and differences in cirrhosis, etiology, and tumor presentation, the superiority of AR over NAR could not be definitively determined.

Table 1. Review of the literature on AR vs. NAR for HCC in the last decade

Author, year	Groups	Patients	Mortality (%)	5-year overall survival	Conclusions
Regimbeau, 2002	AR	30	7	54	AR
	NAR	34	6	35	
Hasegawa, 2005	AR	156	0	66	AR
	NAR	54	0	35	
Kaibori, 2006	AR	34	2.9	52.7	NAR
	NAR	213	1.9	46.2	
Wakai, 2007	AR	95	2	67	AR if >2 cm
	NAR	63	6	59	
Eguchi, 2008	AR	2267	0.7	65.5	AR if 2–5 cm
	NAR	3514	0.8	62.4	
Tanaka, 2008	AR	83	0	54	NAR
	NAR	42	0	61	
Yamazaki, 2010	AR	111	1.8	71	AR if >2 cm
	NAR	98	0	48	

Table 2. Review of the literature on surgical margins for HCC

Author, year	Number of patients	Margin (mm)	Study Design	Findings
Chau, 1997	165	10	Retrospective	Better DFS (>10 mm)
Ochiai, 1999	68	0	Retrospective	No differences
Poon, 2000	288	10	Retrospective	No differences
Matsui, 2007	465	0	Retrospective	No differences
Shi, 2007	84 vs. 85	20	Randomized	Better OS and DFS (>20 mm)

OS = Overall survival; DFS = Disease free survival.

Surgical Margins

The effect of surgical margin status on the survival of patients with HCC has been studied, but controversies persist among surgeons. Some authors have reported that margins smaller than 1 cm or even 2 cm negatively affect long-term survival [8, 9], while others have found opposite results, stating that even 0-mm margins are acceptable [21–23].

A review of the literature on this topic has been presented in table 2: only one randomized controlled study, published by Shi et al. [9] in 2007, is available on this issue. The authors compared HCC patients with 1-cm margins versus those with 2-cm margins and observed a lower recurrence rate in the latter group. The high rate of local recurrence (29%), which is inconsistent with other larger series, and the unclear description of AR and NAR remain major drawbacks of that study. Regarding the latter point, the authors considered certain cri-

teria that should not have been included: tumor location in terms of depth into the liver and tumor location at the edge between two adjacent segments. These two conditions are not contraindications to AR. In these conditions, multiple punctures or compressions of subsegmental/segmental portal branches should be performed to anatomically demarcate the area to be removed.

A concept that should be stressed in discussions of surgical margin status is the relationship between the width of tumor-free margin and tumor size. The risk of satellites increases proportionally with tumor size; in HCCs larger than 2.5 cm, the risk of microsattellites located more than 5 mm away from the tumor burden becomes significant [24]. Therefore, a clear margin should be achieved in the case of tumors larger than 2.5 cm. These findings are consistent with the observation that in the case of HCCs smaller than 2 cm, similar local control can be obtained using either the ablation technique or hepatic resection [25]. However, this should not act as a confounding finding when attention is focused on 0-mm margins at the site of contact between the tumor and a major vessel, whether a glissonian pedicle or a hepatic vein. Under these circumstances, tumor exposure on the cut surface, even when the HCC is larger than 2.5 cm, is acceptable; the possibility of microsattellites is obviously nil at this site and with appropriate surgery under intraoperative ultrasound guidance, the risk of local recurrence is negligible [26, 27]. Conversely, sacrificing the vessels could result in major parenchymal removal and increased surgical risk [28, 29].

AR and Tumor Exposure

From the aforementioned text, it can be considered that the performance of AR does not depend on the achievement of negative margins. Complete microsattellite removal depends on the complete removal of the tumor-containing part, i.e., the entire vascular bed supplying the lesion. An indirect proof is the finding that AR impacts prognosis in patients with tumors larger than 2 cm [17, 18, 20], or in other words, when the HCC has a higher risk of being associated with microsattellites [24] and when ablation is less efficient in providing local control [25]. However, the removal of an entire hepatic segment does not ensure the prevention of tumor exposure. For instance, in the case of an HCC that is located in segment 8 and is in contact with the right and middle hepatic veins at the caval confluence, a full AR of segment 8 will expose on the cut surface the right and middle hepatic veins; the specimen at the level of the detached contact between the HCC and the hepatic veins should have exposed the tumoral surface. As mentioned earlier, the possibility of microsattellites at this site is nil, and the risk of local recurrence becomes negligible if an adequate technique is meticulously applied under intraoperative ultrasound guidance [26, 27]. However, sparing of the vessel by means of tumor–vein detachment minimizes the excision of the liver parenchyma, and it is well established that the prognosis of HCC patients depends much more on the residual liver volume than on the width of the surgical margin [29].

Thus, conceptually, any new lesion occurring in the adjacent segments during the postoperative follow-up period should not be considered as an undetected satellite not removed during surgery, but rather as a distant metastasis (fig. 1). Given the intrahepatic diffusion of HCC through the portal vein system, any metastatic lesion growing in a segment other than the one in which the primary tumor originated should be considered a distant metastatic tumor, regardless of its physical distance from the segment containing the primary HCC.

Fig. 1. Given the propensity of HCC to undergo intrahepatic dissemination through the portal branches (arrows), we recommend that any lesion not supplied by the same segmental portal branch as the main tumor (a) should be considered a distant metastasis rather than a satellite tumor (b), regardless of its location, whether adjacent to (c) or distant from (d) the main tumor and the resection area.

Conclusions

The success of hepatic resection for HCC relies on the accurate balance between the functional reserve of the residual liver and the best local control of the tumor. The review presented herein of the literature, together with the authors' discernment, does not support either AR or large surgical margins *a priori*. The better results obtained with AR than with NAR cannot be definitively attributed to the superior oncological control of AR, although this is theoretically reasonable. The role of AR is probably not very important in the case of HCCs smaller than 2 cm, and moreover, the surgical approach in general is increasingly not being used to treat in such cases. For lesions larger than 2 cm, it seems reasonable that a tumor-free margin of at least 0.5 cm be obtained, unless the tumor is not in contact with a major vessel. However, in this last circumstance, the risk of local recurrence is low, and the outcomes of different technical solutions to spare the vessel should be compared with the worse short- and long-term outcomes of vessel resection before a major hepatectomy is carried out. We believe that tumor exposure is not a contradiction to an AR that is properly carried out with the complete removal of the tumor-containing segment or subsegment. To ensure surgical safety, radical oncological resection with narrow margins, and anatomical, but limited, liver resection, a surgeon's skill in intraoperative ultrasonography is mandatory.

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