Review Article

Surgical management of hepatocellular carcinoma—Western versus Eastern attitude

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Abstract: Hepatocellular carcinoma (HCC) is the most common liver tumour and represents a significant health burden. The different characteristics of the disease in the various parts of the world, as much as economic and social features, explain only partially the great diversity in the treatment options offered to patients in different countries. The most apparent contrast in term of tumour management is between the western and eastern world. Striking differences involve not only the attitude towards indications for liver transplantation or liver resection but also the surgical techniques adopted. Although remarkable signs of progress have been achieved in surgical and pharmacological fields, univocal guidelines are yet lacking, preventing effective comparisons between retrospective studies and clinical trials. This review aims to analyse and compare some of the most relevant and essential traits of the eastern and western therapeutic strategy against HCC.

Keywords: Hepatocellular carcinoma (HCC); liver surgery; liver cancer treatment; liver transplantation

Submitted Oct 07, 2018. Accepted for publication Dec 12, 2018.
doi: 10.21037/tcr.2018.12.28
View this article at: http://dx.doi.org/10.21037/tcr.2018.12.28

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver tumour and nowadays represents the fifth most common tumour worldwide. Opposite to most of the other tumours, the incidence and death rate for HCC has slightly increased in the last decades (1).

Although chronic liver diseases are the leading cause of HCC, the characteristics and natural history of this cancer vary throughout different world regions.

The campaign of vaccination against hepatitis B has significantly reduced the incidence of HBV-related cirrhosis in western countries and some areas of Asia (2). Similarly, the success of the new antiviral drugs (3) holds the well-grounded promise of eradicating the hepatitis C and the HCV-related HCC in the endemic areas of southern Europe and North America. However, new risk factors for chronic liver disease, including obesity, non-alcoholic steatohepatitis (NASH) and diabetes are rising in the modern society, becoming major indications for liver transplantation (LT) in the US nowadays (4).

The variability in the incidence features and natural history of HCC around the world depends mainly on the various etiologies; this situation also drives different management, mirrored in the copious guidelines existing on the treatment of HCC.

A recent review comparing eight guidelines on the surgical therapy of HCC highlighted a different approach not only from West to East but also from country to country, within the same continent (5).

While Asia bases the treatment options on the liver function and, in some areas, also on the number and size

of the lesions, the US and Europe generally adopt the Barcelona Clinic Liver Cancer (BCLC) staging system. Eastern countries are generally more aggressive with both surgical resection and local treatments, saving LT for cases where all previous therapies have failed (2,6). Most of the eastern literature focuses on surgical techniques which allow best oncological outcomes (i.e., anatomical vs non-anatomical resections) and, at the same time, spares liver parenchyma (i.e., portal vein embolisation and ALPPS to increase the volume of the remnant liver).

On the other side, western countries tend to manage HCC according to the EASL guidelines, except for the indications for LT, which are still a matter of debate (7-9). Since deceased donors represent a precious but inadequate resource, the new challenge of the western scientific community is finding the tumour and patient features that define utility of LT in cases of advanced HCC outside Milan criteria, and justice in terms of equal rights for everyone to access the best option of care available (10).

The lack of standard surgical treatment for HCC has an adverse effect as it hampers a valid comparison of the results among the various hepatobiliary centres, and on the clinical practice hinders a choice among different therapeutic options.

These review aims to sum up and describe some of the main differences between "East and West" in the approach to HCC, highlighting not only management differences described in the guidelines but also the technical aspects that have been differently developed.

Very early HCC

For patients with HCC <2 cm and proper liver function (C-P class A), defining BCLC class 0, resection is worldwide the recommended treatment. The possible controversy is whether these lesions should be preferentially resected or ablated. Although no randomised controlled studies exist on this topic, a recent propensity score-matched analysis compared patients with very early HCC undergoing liver resection (LR) or radiofrequency ablation (RFA). The results showed a better outcome in the LR group, with 5-year recurrence-free survival and overall survival respectively of 80% and 48% in the group of LR, compared to 66% and 18% in the group of patients treated with RFA (11). Adherence to the BCLC algorithm is observed in eastern and western countries for what concerns the treatment of very early HCC (2,12).

Different management may be needed in cases of very early HCC in patients with C-P class A but with clinically evident portal hypertension. Although LR remains the treatment of choice, the risk of postoperative liver failure is considerable. A reliable assessment score is the ALBI grade, an index based on the objective values of bilirubin and albumin. The ALBI grade showed a valuable prognostic accuracy in predicting overall survival of patients in the same C-P score, undergoing LR for HCC (13). This tool has proved effective particularly in the setting of very early HCC in patients with C-P class A and portal hypertension (14).

Early HCC

LR

For the treatment of early HCC, in cases of single lesions and portal hypertension, the BCLC algorithm recommends LT or RFA whenever LT is contraindicated.

Single nodules within Milan Criteria (between 2 and 5 cm) are treated with LR from most eastern centres, for which the major issue of debate is which therapy represents the best option between LR and RFA. Several randomised controlled studies, published by eastern groups, have compared LR and RFA, defining slightly better results for LR over RFA, particularly respect to the higher risk of residual disease for RFA (15-18). A recent randomised controlled study has highlighted the equivalence of LR and RFA in term of overall and disease-free survival for HCC within Milan criteria (19). However, the available studies have not compared the two techniques in a subset of patients with portal hypertension, leaving the doubt that in cases of slightly impaired liver function RFA may be a better option than LR. Interesting studies have been performed by the group of Bologna, who retrospectively investigated this topic through sensitivity and a probabilistic analysis, finding a survival advantage for RFA compared to LR for patients with single small HCC in the presence of partially compromised liver function [Model for End-Stage Liver Disease (MELD) ≥10]. With an increasing degree of liver dysfunction, the benefit of LR decreases and RFA achieves better survival (rates) in the case of larger tumours (20).

Single large HCC lesions (greater than 5 cm) are generally treated with LR when liver function allows the operation. There are several monocentric reports around the world (eastern and western countries) describing the success of surgical resection of large single HCC lesions (up to 10 cm in diameter) without macrovascular invasion

in patients with C-P class A and preserved liver function (21-27). The attitude is different toward multinodular HCC within the stage A of BCLC algorithm (up to 3 lesions <3 cm). While western guidelines recommend LT or RFA, when transplantation is contraindicated, eastern countries perform LR in these cases, with better overall and recurrence-free survival compared to RFA (28).

LT

Western regions too have started adopting more and more often LR over LT due both to the lack of available organs and to the high rate of dropout during the waiting list (29). Although no randomised controlled trials have been published, several retrospective studies from western centres have compared LR and LT for early HCC, showing an overall survival advantage for LT over LR. The results have been controversial, possibly because of selection bias of better liver function in the groups of LR, and the lack of listing criteria standardisation for LT (30-33). However, a meta-analysis published on the comparison of resection vs transplantation for early HCC, including studies with an intention to treat analysis, concluded for comparable overall survival for both treatment options in patients in C-P class A with early-stage HCC (34). The main problem with LR in case of early HCC remains the high rate of post-operative recurrence; a common strategy to overcome this issue is to adopt the salvage transplantation when HCC recurs after resection.

After the initial enthusiasm among many European centres, more recent papers have highlighted the drawbacks of this procedure, mainly the higher rate of complications, particularly bleeding, for salvage LT versus primary LT (35,36). Moreover, when intention to treat analysis was performed, higher overall survival for primary LT versus salvage LT was observed, undoubtedly due to the frequent recurrence of HCC outside Milan criteria after the initial resection, which precludes a subsequent LT (37). Although controversial results have been reported in the last decade, a meta-analysis of primary versus salvage LT has shown comparable results in term of overall survival (38). The salvage transplantation bears many advantages: first sparing organs, an issue of great worldwide importance nowadays, transplanting only those patients who recur after resection. Secondly, the waiting time between resection and transplantation, while on one hand causes dropout when a recurrence outside Milan criteria occurs, on the other hand, allows a better definition of the biological nature of the tumour, in case of early and aggressive recurrence of HCC, which may exclude the option of LT.

Intermediate HCC

Intermediate HCC stage B, multinodular tumours in a patient with normal or impaired liver function (C-P class A–B) can only be considered for chemoembolisation, according to the BCLC algorithm.

Several monocentric reports have been published in the last decade, describing the real-world approach to multicentric tumours, which detaches significantly from the BCLC recommendations.

In 2015 a systematic review and meta-analysis was published comparing the overall survival after hepatic resection and transarterial chemoembolization (TACE); in this review, one randomised clinical trial was also included (39). This paper witnessed how common the surgical strategy is for intermediate stage HCC mainly but not exclusively in eastern regions, and how LR yields significantly better overall survival compared to TACE.

This result was confirmed in later meta-analysis and reviews (40,41). When LR was applied for the treatment of multinodular HCC, median survival of 37 months and 5-year survival of 35% were achieved, which is more than the 18 or 28 months that had been historically reported with TACE, on which the BCLC algorithm is based (42-44).

However, a prognostic difference exists in term of worse outcome for patients who present for LR with more than 4 lesions, who experience 5-year survival of 31%, compared to 75% for those who have up to 3 lesions <5 cm and 63% for those up to 3 lesions ≥5 cm respectively (45). This result has been acknowledged and integrated into the Asia-Pacific clinical practice guidelines of 2017 for which LR is recommended for HCC lesions of any size up to the number of 4 (2).

Advanced HCC

The role of surgery has been acknowledged not only for intermediate stage HCC both in eastern and in western countries, but also for large lesions associated with macrovascular invasion, defined as advanced HCC. A recent review has summoned up the evidence present in the literature about the worldwide experience on both multinodular HCC and HCC with portal vein tumoral thrombosis (41).

Several western and Asian retrospective studies have

reported a 5-year survival as high as 20% after hepatic resection in cases of HCC with associated portal vein thrombosis (46-51), significantly better than either TACE or sorafenib, which is the recommended treatment option according to the BCLC algorithm for stage C HCC. Notably, not all types of portal vein thrombosis bear the same prognostic value (52). In particular, type I and II thrombosis defined respectively as thrombosis extending distal to the second-order branches or involving the second-order branches, have a much more favourable prognosis (53,54). When the thrombosis extends to the first-order branches (type III) or the main portal vein/the contralateral branch (type IV), a thrombectomy should be associated with the hepatic resection. In these cases, the high mortality and recurrence rate decrease the overall survival to less than 15%, encouraging the adoption of TACE *vs.* surgery.

While studies from Europe and USA have reported these isolated experiences, EASL-EORTC guidelines still recommend Sorafenib for HCC with macrovascular invasion. Based on these results, Asia-Pacific guidelines have recently included resection as an option for the treatment of advanced HCC; according to these guidelines, HCC with macrovascular invasion that does not reach the first order branches, is treated with surgical resection according to expected post-operative liver function (55).

LT

LT as a method of HCC therapy has crossed and still covers several BCLC HCC stages.

Although the initial experiences with LT as HCC therapy yielded ominous results, at the end of 90s Mazzaferro reported an extraordinary 4-year overall survival exceeding 80% adopting some strict criteria (single lesion inferior or equal to 5 cm or up to 3 lesions, none exceeding 3 cm), later named Milan criteria, for listing patients in waiting list for LT (56). From that turning point, HCC became one of the main indications for LT, mainly when MELD exception points were assigned to patients with HCC in order to lower the rate of dropout from the waiting list for tumour growth.

Although Milan criteria are still adopted worldwide, some issues are on the debate. On one hand, Milan criteria are too strict and do not include patients who may have a survival advantage from accessing the waiting list for LT. On the other hand, some patients who fall within Milan criteria may equally benefit from LR leaving the scarce resource of organs from deceased donors to patients with liver failure, who do not have other therapeutic options other than LT.

Criteria expansion

Many groups, mainly from western countries, have looked for expansion of the Milan criteria for listing patients for LT. After the experience of the University of California San Francisco (57), other groups analysed the outcome of patients who underwent LT and in which the gross pathology showed a tumour burden beyond Milan criteria. Among these reports, Mazzaferro performed a multicenter retrospective study including patients who were transplanted outside the Milan criteria. He found that the cumulative size more than the number of lesions, and the microvascular invasion were more predictive of post-transplantation disease recurrence and low survival. The patients who were included in the "up-to-seven" rule (the sum of number and size of all lesions was 7) had an overall survival similar to those who were transplanted within Milan criteria (58). Thanks to these results, the online Metroticket calculator was created, which allows predicting 3- and 5-year overall survival with known tumour features (lesion number and size, and presence of microvascular invasion). However, the development and validation of the Metroticket calculator were performed accounting for factors available on the pathology study. The retrospective nature of the tool limits its utility for prognostic purposes.

More recently, the Liver Transplantation French Study group developed a prognostic model which combined α-fetoprotein, tumour size, and number of lesions and was highly predictive of tumour recurrence and death (59). Notably it included all features that can be acknowledged before the transplantation. Recently an Italian-Chinese multicentre study developed a model based on pre-transplant features (level of AFP, tumor size and number at radiology), to determine the risk of death from HCC-related factors after LT (60). The main steps in the HCC criteria expansion for LT are listed in *Table 1* (57-59,61-67).

Downstaging

From the West, and in particular from the UCFS, came the idea of downstaging HCC, through resection or loco-regional therapies, in order to bring an intermediate or advanced stage cancer back within acceptable criteria for LT (68). The group achieved an intention to treat 1- and 5-year survival respectively of 89% and 56% (69). Recently a review has reported the results of all the studies published

Table 1 Main protocols of expanded criteria for liver transplantation for hepatocellular carcinoma

Denomination	University	Year	Criteria
UCSF criteria (57)	California-San Francisco, USA	2001	1 lesion ≤6.5 cm or 2–3 lesions ≤4.5 cm with total tumor ≤8 cm; no extrahepatic disease; no macrovascular invasion
Dallas (61)	Baylor University Medical Center, Dallas, USA	2007	Largest lesion <6 cm; No. of lesions <4
5-5 rule (62)	University of Tokyo, Japan	2007	No. of lesions ≤5; maximum diameter ≤5 cm
Asan criteria (63)	University of Ulsan College of Medicine, Seoul, Korea	2008	Largest tumour diameter ≤5 cm; lesion number ≤6; no macrovascular invasion
Up-to-7 (58)	University of Milan, Italy	2009	Sum of diameter of the largest tumour and number of lesions =7; no microvascular invasion
Kyushu criteria (64)	University of Kyushu, Japan	2009	All tumours <5 cm; DCP <300 mAU/mL
Kyoto criteria (65)	Kyoto University, Japan	2010	Number of lesions ≤10; diameter of lesions ≤5 cm; PIVKA-II ≤400 mAU/mL
AFP model (59)	Groupe Henri-Mondor, Créteil, France	2012	Score <2 low risk of recurrence; largest diameter: ≤3: 0 points, 3–6: 1 point, >6: 4 points; No. of lesions: 1–3: 0 points, ≥4: 2 points; AFP: ≤100: 0 points, 100–1,000: 2 points, >1,000: 3 points
Total tumour volume (66)	University of Alberta, Edmonton, Canada	2015	≤115 cm^3 and AFP ≤400 ng/mL; no extrahepatic disease; no macrovascular invasion
Toronto criteria (67)	University of Toronto, Canada	2016	Any size and number of lesions; no cancer-related symptoms; no extrahepatic disease; no vascular invasion; no poorly differentiated tumour

IVKA-II, protein induced by vitamin K absence or antagonist-II; DCP, des-gamma-carboxy prothrombin.

on downstaging, mainly from Europe and the US, only one from South Korea (70). The small sample of each study and in particular the heterogeneity of the population and the criteria for inclusion and restaging, make it difficult to draw definitive conclusions. When the downstaging protocol, the modality and delivery techniques were explicitly stated as much as the waiting time from the downstaging to the enrollment in the waiting list, the reported outcome was good, with up to 90% 5-year survival (71).

The utility of downstaging has been the subject of much debate since the evidence of a beneficial effect is inconsistent. As a result, at present, the European Association for the Study of the Liver did not reach a consensus on expanded criteria for LT in HCC due to moderate grade of evidence and weak grade of recommendation; EASL suggests patients beyond Milan criteria be considered for LT after successful downstaging to within Milan criteria, only within defined protocols (72).

It is notable that response to downstaging represents a selection instrument nowadays for refining priority in patients with HCC (73,74).

A new therapeutic tool to treat advanced HCC is the selective internal radiation therapy (SIRT), also called radioembolization, and it has been used in several centres in a setting of "super down-staging protocol". Few studies are still available (75,76) but it seems to have significant future clinical applications, whether in a transplantation background, and/or in just a curative/palliative setting.

We depicted in *Table 2* the main protocols of downstaging described worldwide (77-92).

Bridge therapies to transplantation

When talking about bridge therapies, we refer to the treatment of patients while on the waiting list for LT. These treatments are the same used for downstaging and as therapy (potentially curative or palliative) for patients not suitable for LT. Bridge therapies are needed as patients with HCC are at risk of tumour progression while waiting for LT, can eventually drop-out.

Several studies have demonstrated significant advantages of neoadjuvant therapies in reducing this risk due to tumour progression (29,69,71,93,94). In addition to limiting the drop-out risk, these bridging therapies reduce post-LT

Table 2 Main protocols of down-staging for liver transplantation for hepatocellular carcinoma

Author	Center	Year	Criteria for entering the down-staging protocol
Majno (77)	Hospital Paul Brousse, Paris, France	1997	Tumor size >3 cm; any number
Graziadei (78)	University Hospital Innsbruck Austria	2003	Outside Milan criteria
Otto (79)	Gutenberg University, Mainz, Germany	2006	Outside Milan criteria
Millonig (80)	University Hospital Innsbruck Austria	2007	Outside Milan criteria; within UCSF criteria
Yao (81)	University of California, San Francisco, USA	2008	One lesion between 5 and 8 cm; up to 3 lesions between 3 and 5 cm, total tumor diameter <8 cm; up to 5 lesions <3 cm, total tumor diameter <8 cm
Ravaioli (82)	University of Bologna, Italy	2008	One lesion ≤6 cm; two lesions ≤5 cm; up to 5 lesions ≤4 cm, total tumour diameter ≤12 cm (Bologna criteria)
Chapman (83)	Washington University School of Medicine, St Louis, USA	2008	Outside Milan criteria
Heckman (84)	University of Pittsburgh, USA	2008	Not specified
De Luna (85)	Stanford University, School of Medicine, Stanford, USA	2009	Outside Milan criteria
Lewandowski (86)	Northwestern University, Chicago USA	2009	UNOS T3
Barakat (87)	St. Luke's Episcopal Hospital, Houston, USA	2010	Outside Milan and UCSF criteria
Jang (88)	The Catholic University of Korea, Seoul, South Korea	2010	Outside Milan criteria
Green (89)	University of Colorado Hospital, Aurora, USA	2013	Outside Milan criteria
Bova (90)	I Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT), Palermo, Italy	2013	Outside Milan criteria; no tumour thrombus; no metastases
Pracht (91)	Comprehensive Cancer Center Eugène Marquis, Rennes, France	2013	Lobar HCC; ipsilateral portal vein thrombosis
Hołówko (92)	Medical University of Warsaw, Poland	2015	Outside Milan criteria

cancer-related mortality, particularly when a waiting period of over six months is expected from listing (60,73,74,95).

However, more recent papers have failed in confirming the importance of bridging loco-regional therapies in reducing post-LT mortality and the risk of dropout for tumour progression. A meta-analysis of studies about patients treated with down-staging or bridge therapies to LT was published this year by Kulik *et al.* (96). The quality of evidence was very low because bias, inconsistency and imprecision in the several considered studies; however, the meta-analysis reported a nonsignificant trend towards improved waitlist survival and post-transplant outcomes for patients undergoing bridge therapies. For patients with stage T1 HCC the risk for dropout at 6 months is as low as 5%, but it rises to 30% at 2 years and a half with an 88% risk of progression to stage T2.

For patients with stage T2 HCC treated with bridging therapies to LT, the risk of waitlist dropout for tumour progression or for all causes was non-significantly reduced compared to no therapies. The only cluster of patients where significant improvement of outcome was achieved with pre-transplantation loco-regional therapy was that of waitlist patients with stage T3 HCC, who underwent

down-staging; they showed better 1- and 5-year survival, compared to patients who did not receive any treatment.

Survival benefit

Surely the issue of defining the best allocation system for patients with HCC is a challenge for the international scientific society. At the core of this problem is the scarce resource of available organs that need to be shared among all patients in the waiting list. When dealing with this topic, in addition to the principle of not harming, we need to consider the principles of justice and equity in access to the cure for everyone. In 2009 the concept of transplant benefit was first introduced in the setting of LT, described as the difference from the survival obtainable from the time of listing and the survival achievable with non-transplantation options (97). Ideally, the limited organs available from deceased donors should be allocated neither to patients on the waiting list with the shortest expected survival (urgency) nor to those with the longest expected post-transplant survival (utility) but to those with the greatest transplant benefit. In the last decade, several papers have been published on this topic, but the lack of an accurate predictor of post-LT transplant benefit has prevented the integration of the transplant benefit in a system for organ allocation (98-100).

It seems obvious that a perfect allocation system has to consider some local factors, which are different from country to country, in particular, the availability of organs per population and the rate of HCC over other etiologies for listing. Even more importantly, the biology of the tumour should be included in a model that encompasses the response of the tumour to the locoregional therapies and the behaviour of the tumour during the time in the waiting list (101). Recently several European, and particularly Italian hepatobiliary centres have focused on the definition of a model that could fit for this very challenging purpose; these models are still to be validated in multicentric settings (102).

The importance of the biology of cancer has been explored by the Toronto group, who showed that poor tumour differentiation at pathology and HCC-related symptoms define patients with advanced cancer beyond Milan criteria, who may benefit of LT with outcome comparable to patients within Milan criteria (67).

Living donor LT (LDLT)

LDLT was first performed in 1988, and since then it has spread worldwide with different success. It is a double demanding procedure as both transplantation in the recipient and hepatectomy in the donor bear considerable morbidity and mortality risks, which range between 2% and 10% for the donor (103-105). Due to the low incidence of deceased donation in Asia, and particularly in Korea, LDLT represents a significant resource for LT in eastern countries, while West lags in the spread of this technique even in highly specialised hepatobiliary centres (106,107). At present, the most significant reported experience of LDLT is in Asian countries where eight times more LDLT have been performed compared to the western world (108).

The undisputed advantage of LDLT is the prompt availability of an organ for a recipient who would otherwise wait a long time before transplantation from the deceased donor pool. LDLT seems the perfect solution for patients with HCC at risk of dropout during waiting list, and it is, in fact, the leading indication for LDLT in the adult population worldwide (67,109,110). In the last decade, as the experience was growing, also the HCC features for enrollment in the LDLT were expanded beyond Milan criteria from Japanese and Korean University centres (62,63,111-113), reporting excellent results of over 70% 5-year overall survival in most of the series.

The acceleration towards transplantation may be an advantage and a drawback at the same time, as the reduced waiting time before LDLT may not allow adequate observation of the course of the disease, and therefore impair the outcome of the procedure due to an increased rate of HCC recurrence after transplantation. A multicentric American study published in 2012 compared the outcome of patients transplanted from living donors versus others transplanted from deceased donors (114). The results reported an increased rate of HCC recurrence after LDLD, fostering the fear that LDLT was not suitable for HCC. However, the two groups were not homogeneous, as the recipients of living donors had more advanced tumours, more often outside Milan or UCFS criteria. A later multicentric French study contradicted this theory reporting improved 5-year intention to treat survival in LDLD compared to LT from deceased donors (115). The rate of HCC recurrence was similar among the two groups; therefore the type of transplantation was not a predictor of

Table 3 Main differences between deceased and living donor liver transplantation for HCC

Category	Pros	Cons
LDLT	Short wait before transplantation reduces the risk of dropout for extended HCC; does not affect the pool of organs from deceased donors	Morbidity and mortality risk in the donor; demanding procedure in the recipient
DDLT	The time in waiting list can allow a better biological definition of the tumour; easier procedure	Risk of dropout in the waiting list; need to consider the transplant benefit

LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation.

recurrence while macrovascular invasion, tumours outside MC and AFP model score higher than 2 were.

A summary of the main pros and cons of living donor versus deceased donor LT is reported in *Table 3*.

Anatomic *vs.* non-anatomic resection

When dealing with more technical aspects of the surgical treatment of HCC, we cannot neglect the long-standing debate on anatomic versus non-anatomic LR.

Conventional non-anatomical LR aims to excise the tumour with a rim of tumour-free parenchyma around the lesion. Through this procedure, minimal healthy liver is removed with the surgical specimen, which is paramount in cirrhotic patients to avoid postoperative liver failure (116). Several authors, on the other hand, claim the importance of anatomic resection, which is the removal of the tumour together with the draining portal veins and the corresponding hepatic territory, which is a considerable amount of healthy liver parenchyma (117,118). The reason for this surgical technique is to provide a better oncological control of tumoral cells which may have spread in the vascular system and to prevent the development of satellite nodules along the portal pedicle.

The outcome of anatomic versus non-anatomic LR in cirrhotic patients has been analysed in several retrospective observational reports, but no prospective randomised trials are available at the moment. However, the contradictory nature of the published evidence makes it difficult to conclude the best surgical approach.

Recently Tan *et al.* performed a systematic review of the literature on this topic, almost exclusively from eastern countries (119); the only exception being Italy with one contribution from the oncological group of Turin and one multicentric study involving the group of Bologna and Eastern Hepatobiliary Surgery Hospital, Shanghai (120,121). The result of the meta-analysis showed that anatomical resection improved both disease-free and overall survival compared to non-anatomical resection. The beneficial effect was more evident in patients with small solitary HCC. However, the surgical technique did not influence the late HCC recurrence, possibly reflecting the advantage of anatomical resection to prevent local recurrence when tumorogenic cells have spread from a single lesion along the portal pedicle. This beneficial effect was not evident in cases of pre-operative multicentric nodules or single lesions under 3 cm.

Video-laparoscopy *vs.* open

The mini-invasive approach bears many potential advantages for cirrhotic patients who need a surgical resection for HCC. First of all, the small incisions are less prone to ascitic infiltration and consequent dehiscence and herniation. Secondly, less invasive surgery reduces the physiological stress response in the patient, although this effect has not been well studied in a compared analysis. Finally, the laparoscopic approach decreases the hilar dissection and liver isolation creating fewer adherences than open surgery; this considerably reduces the bleeding and the risk of complications during a later surgery, if HCC recurred. However, laparoscopic LR is a demanding procedure, for many technical reasons; the difficult hemostasis at the transection plane, the risk of air embolism, and limited visibility of deeper and posterior regions of the liver are among the main difficulties for surgeons (122).

Not all the types of LRs have the same level of complexity. When the initial laparoscopic LRs were attempted in the 1990s, anterolateral segments and left lateral sectionectomy were first approached, and hemi-hepatectomies were performed later. Sectionectomies, segmentectomies and partial resection of segments I, VII and VIII have been reported in the last decade with success (123).

In the attempt of implementing and standardising the laparoscopic approach for LR for malignancies, two international consensus conferences were held in 2008 in 2015, discussing the safety of the procedure and technical surgical aspects (124).

Table 4 Video-laparoscopy (VLS) versus open surgery for resection of hepatocellular carcinoma

Category	Pros	Cons
VLS	Lower rate of incisional dehiscence; little hilar dissection; fewer adherences in case of the following surgery; faster recovery	Difficult hemostasis and biliostasis; Difficult identification of the transection line; Risk of air embolism; Limited vision of posterior segments
Open	Easy access to any segments; major hepatectomies are possible; feasibility of vascular reconstruction	Longer hospital stay; more extended dissection and risk of adherence; higher risk of incisional dehiscence; more post-operative risk of ascites

A recent meta-analysis reviewed the comparative studies available in the literature, mainly from Asian groups, between open and laparoscopic LR for HCC. The meta-analysis showed that laparoscopic technique is superior concerning lower intraoperative blood loss and the requirement for blood transfusion, larger pathologic resection margins, increased R0 resection rates, and shorter length of hospital stay, with equal recurrence rate, overall and disease-free survival (125).

The benefit of minivasive major LRs still needs to be reinforced by prospective clinical trials. Although the highest number of studies on laparoscopic resections comes from Asia, the common direction from eastern and western countries is towards the diffusion of laparoscopic application for HCC resection. In particular, registries have been prospectively started in various western countries (126), and randomised control trials are open worldwide (127).

The features of video-laparoscopic versus open LR are represented in *Table 4*.

Portal vein embolization (PVE) *vs.* associating liver partition and portal vein ligation (ALPPS)

PVE consists of occlusion of a branch of the portal vein feeding the hepatic lobe where the malignancy is located. The procedure aims to cause the hypertrophy of the lobe contralateral to the embolised portal branch, with the subsequent increasing future liver remnant and reduced risk of postoperative liver failure.

It was initially employed by Makuuchi to increase the safety of major hepatectomy in case of hilar bile duct malignancies, but then PVE has been later adopted also for other forms of malignancies. Several reports have been published in the last decade about the role of PVE to allow major resection for large unilobar HCC. Asian groups are the leading authors in this field since, as previously discussed, they strongly support the role of LR in cases of even advanced HCC.

A systematic review recently reported good long-term survival after resection with PVE for different types of malignancies; HCC had the lowest rate of dropout of the resection for disease progression after PVE, and the highest 5-year survival rate, ranging between 30% and 55% (128,129).

However, PVE is not the only technique to increase liver resectability in case of an expected low future liver remnant. ALPPS was first described by the German group from Regensburg in 2012 (130). It is a two-stage procedure, indicated in case of bilobar lesions. In the first step, the liver parenchyma is transected along the intended line of resection and the future liver remnant cleaned from all tumour tissue through wedge resections. Finally, the surgeon ligates the portal vein branch feeding the lobe with the major tumoral burden. The second step is performed after 1–2 weeks when the liver portion excluded from portal flow is removed, generally with a major hepatectomy. The liver transection associated with the portal vein ligation elicits a significant hypertrophic response and a higher rate of success in finalising the second step of the procedure.

In the last few years, the procedure has spread worldwide in western but also eastern countries and adopted for all sorts of malignancies. Until now only case reports and small series have been reported on the short and long-term survival of cirrhotic patients undergoing ALPPS. Although good results have been initially obtained in patients with HCC in term of overall survival and success of completion of the procedure (131-133), long-term results are not yet available, and the few randomised controlled trials started on this topic are not yet concluded.

A systematic review and meta-analysis, recently published on the use of ALPPS for HCC, reported a higher rate of postoperative mortality and morbidity, often related to liver failure (134).

The procedure of ALPPS is a major surgical procedure, associated with a high rate of complication. It is a very "young" procedure, first adopted six years ago. Some

Table 5 Comparison of ALPPS versus PVE in the treatment of HCC

Category	Pros	Cons
PVE	Longer experience and follow up; lower incidence of postoperative morbidity and mortality	Higher risk of insufficient liver hypertrophy after the procedure
ALPPS	Indicated for bilobar lesions; greater liver hypertrophy and higher chances to proceed to complete the second stage; potential for a mini-invasive procedure	Young procedure with little follow-up; higher morbidity and mortality

PVE, portal vein embolisation; ALPPS, associating liver partition and portal vein ligation for staged hepatectomy.

technical aspects have already been modified in order to make the operation less invasive and possibly reduce the complications, but more accurate and reliable diagnostic tools are still needed to better predict the potential for liver hypertrophy and define the best timing for the second, resective stage.

We briefly compared the advantages and cons of the two described procedures in *Table 5*.

Conclusions

As discussed in the previous paragraphs, the management of HCC considerably differs in western and eastern centres.

Endemic and social differences exist between the West and the East. The higher prevalence of HBV infection in China and India accounts for the higher incidence of advanced HCC in this population with a more preserved liver function. This situation partially explains the more aggressive surgical attitude of eastern countries. The opposite occurs in the US and West Europe, where the prevalence of HCV-related cirrhosis, causes the development of multiple small HCC lesions. Western groups have always tended towards LT as the best cure option for patients with HCC developed on cirrhotic livers. Opposite to what is still recommended in most western guidelines, we have seen the effort of the international community to expand the surgical indications through advanced and mini-invasive approaches. At the same pace, and in more recent times, US and Europe in particular, have focused on optimising the insufficient resource of organs from deceased donors towards the patients who may benefit the most from this treatment. This is a very fascinating, but still unravelled field of discussion which, by now, remains limited to debates on scientific papers and in conferences.

LT from living donor (LDLT) is the section in which both America and Europe still lag far behind. Traditionally, eastern countries have adopted LDLT specifically for the treatment of HCC, and remarkably implemented the technique. Nowadays in some realities such as Korea, LDLT is the primary source of LT and the experience in the field is extremely high.

Although acknowledging the raised level of attention mandatory for the donor safety, certainly the implementation of LDLT programs in western countries, and particularly in Europe, should be strongly encouraged in order to meet the growing need of organs for transplantation.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Giovanni Brandi; Francesco Tovoli) for the series "Primary Liver Cancer" published in *Translational Cancer Research*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.12.28). The series "Primary Liver Cancer" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Neri F, Maroni L, Ravaioli M. Surgical management of hepatocellular carcinoma—Western versus Eastern attitude. Transl Cancer Res 2019;8(Suppl 3):S245-S260. doi: 10.21037/tcr.2018.12.28

