



Current and Future Challenges in the Surgical Treatment of Hepatocellular Carcinoma: A Review

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Challenges in the treatment of hepatocellular carcinoma Hepatocellular carcinoma (HCC) represents one of the most frequent types of cancer worldwide. Surgery, although only a part of the armamentarium against HCC, represents the cornerstone in the management of this aggressive disease. This article will review the current and future challenges in the surgical management of HCC, with a special emphasis on the following areas: (1) the evolution of staging of the disease and the importance of the biological nature and behavior of HCC, (2) the effort to increase resectability, (3) technical innovations and the role of image-guided surgery, and, finally, (4) the role of liver transplantation in the continuum of care for these patients. Although by no means an exhaustive list, the issues mentioned above represent some of the most promising prospects for significant progress in the management of HCC.

Key words: Hepatocellular carcinoma – Image-guided surgery – Liver transplantation – Resectability

The incidence of hepatocellular carcinoma (HCC) has risen significantly in the United States in the last decade, only to be surpassed by the increased incidence in East Asia and sub-Saharan Africa because of the high prevalence of hepatitis B in that area.^{1,2} In other parts of the world, such as North America, Europe, and Japan, the main culprit appears to be the high prevalence of chronic

hepatitis C infection, together with confounding factors, such as alcohol abuse, nonalcoholic steatohepatitis, obesity, and tobacco use.^{3–5} The common theme is the association between liver cirrhosis and HCC, with 80% of HCC cases being in cirrhotic livers.⁶ Although the exact mechanism has not been fully elucidated yet, it may have to do with changes in the normal hepatic architecture seen in cirrhosis

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or with damage caused by the viral DNA in the cases of hepatitis infection, both representing a cancerous transformation signal.

Given the complexity of the disease, it should come as no surprise that its treatment is multimodal and requires the cooperation of multiple specialties. Even so, surgery remains the cornerstone of the management of HCC, as it has the unique ability to provide a therapeutic option. The 2 main curative surgical therapies are liver resection and orthotopic liver transplantation (OLT). Even with careful patient selection, recurrence and metastatic disease remain the 2 main problems encountered in liver resection, with OLT having to deal with the additional obstacle of the limited number of available donors. Other treatments, such as chemo-embolization or radiofrequency ablation, may be able to limit the disease in certain situations or act as bridging therapies, although overall the results cannot be compared with those of resection or OLT. The limitations mentioned above serve to underscore the challenges facing hepatic surgery, as well as to identify the areas where the research efforts should be focused. In this article, the areas that will be reviewed represent promising prospects for progress in the surgical management of HCC.

Current and Future Challenges

Staging and the biologic behavior of the disease

It is very interesting, and potentially indicative of the unpredictable nature of the disease, that there is not a universally accepted staging system for HCC. There are several different ones, each one looking at different aspects of the disease, such as the clinical and radiologic findings prior to treatment versus the histopathology after treatment. They include the American Joint Committee on Cancer/Union Internationale Contre le Cancer Tumor-Node-Metastasis (AJCC/UICC TNM) staging system, the Okuda system, and the Cancer of the Liver Italian Program (CLIP) staging system, with all of them having shortcomings.⁷⁻⁹ Namely, the AJCC/UICC TNM system does not incorporate the underlying liver disease, which is what the Okuda and the CLIP systems have attempted to do, while at the same time not being accurate with early stage disease. The one with the highest acceptance appears to be the Barcelona Clinic Liver Cancer (BCLC) system, which takes into account total cancer load, the stage of the cirrhosis, and the patient's functional status, with the goal of determining expected survival, as well as proposing possible treatment.^{10,11} The fact

that it has been externally validated and that it provides a connection between the stages and the different treatment modalities serves to increase its popularity.¹² Even so, it fails to incorporate the many nuances of the biologic behavior of HCC, which is the reason for the ongoing research effort toward identifying a molecular classification for HCC.

There have been significant research efforts, such as the extensive genomic and transcriptomic characterization of tumors from hepatitis C virus-positive patients.¹³ That multinational study showed that high-level copy number gain of 6p21 represents one mechanism for increasing Vascular Endothelial Growth Factor A (VEGFA) expression, which can play a role in the response of the tumor to the VEGF inhibitors or receptor agonists. Furthermore, other gene expression studies have analyzed patients with HCC of different etiologies and at different stages of the disease and have identified five major molecular classes of HCC.¹⁴⁻¹⁷ Despite these exciting findings, linking them to survival outcomes is still at a very early stage.¹⁸ Others have used the Total Tumor Volume and the AFP value as a way to stage patients and identify the best candidates for OLT.¹⁹ This concept has been extensively validated even in large databases; yet it still does not include a lot of the known important prognostic factors, such as vascular invasion or the amount of necrosis in the tumor, thus limiting its applicability. Perhaps one of the most significant advances is the identification of microRNA and its role in hepatic carcinogenesis—a complex one indeed, as different microRNA profiles have been reported to be either upregulated (such as miR-221 and miR-181) or downregulated (such as miR-122 and miR-26) in HCC.^{20,21} What may be seen as discrepancies in the role of microRNA should be considered as the result of both HCC heterogeneity and the versatile biologic nature of microRNA, which are also affected by the existing microenvironment. In addition, testing and experimental circumstances can affect the results, thus introducing significant challenges.^{22,23}

Despite these challenges, it is apparent that we are moving into a new era where staging and, possibly, treatment decisions will be based on the molecular classification of the tumor as much as they are based on the clinical and radiologic appearance. The reason for this is the appreciation that is being acquired for the significance of the biologic behavior and nature of HCC.

How to increase resectability of HCC

Increasing resectability of HCC represents an area of increased research interest, as any success in that area could lead to a higher number of people being able to undergo a therapeutic treatment. There are 2 steps in this process. The first one involves evaluating the existing hepatic reserve, both in terms of quantity and quality, so as to see how extensive a resection the hepatic remnant would allow. In terms of the quality, this can be assessed either clinically or radiologically. The clinical assessment can be a direct one with a liver biopsy, or an indirect one using the synthetic function (International Normalized Ratio (INR), platelets, albumin) or signs and symptoms of cirrhosis, such as portal hypertension and varices. Along these lines, it is very important that we have a sense of the status of the hepatic chronic disease, if one exists, and whether the patient has undergone any treatment and what the response has been. Regarding the radiologic estimation of the hepatic reserve, this is mainly based on computed tomography (CT) volumetry, which could even be performed by the surgeon on a personal computer with the use of the Digital Imaging and Communications in Medicine (DICOM) system. Essentially, volume-wise, an adequate hepatic remnant can be considered as one of 25% of the existing liver in the case of normal hepatic function, or 40% in the case of cirrhosis.²⁴

However, once the existing hepatic reserve has been determined, the next step is how to increase it, so as to be able to achieve a more extensive resection. The 2 main methods increase the hepatic reserve are portal vein embolization (PVE) and the more recent technique of associating liver partition with portal vein ligation for staged hepatectomy (ALPPS).²⁵ Preoperative portal vein embolization, first introduced in clinical practice by Makuuchi in 1982 for the treatment of cholangiocarcinoma, is based on the theory that occluding the flow in the portal vein branch on the side of the tumor leads to atrophy of that side and, more important, hypertrophy of the other side up to 20% to 40%, which will eventually represent the hepatic remnant after the resection.^{26,27} This will allow for a staged procedure and represents an excellent strategy for a small hepatic resectability or bilobar disease. The added advantage is that it can be done percutaneously, although it certainly represents a technically challenging procedure requiring a very experienced interventional radiologist. As widely as it is used, the detailed mechanism is not fully understood, and

there are some concerns about whether it can stimulate growth of existing tumor as part of the contralateral hypertrophy. The ALPPS procedure represents an extension of this notion, as it consists of an in situ liver resection combined with portal vein ligation as the first stage, leading to growth of the future liver remnant, and thus allowing a second stage within a short time period, where the part of the liver with the tumor is resected.^{28,29} The advantage of the ALPPS procedure is a shorter time period between the stages, compared with the PVE, in addition to decreased surgical risk in the second operation, as the majority of the dissection has already been performed. Even so, we need to remember that the ALPPS procedure still needs to be fully evaluated, and that at the present time, PVE (preferably percutaneous) followed by the resection remains the gold standard in the case of a small hepatic remnant.³⁰

Another option increasing in respectability is using the downstaging strategy. Specifically, although the success of the Milan criteria is universally accepted, as we will see in the section discussing orthotopic liver transplantation for HCC, there remains an active effort to expand these criteria in order to increase the number of patients that would benefit from curative, rather than palliative, treatments. Downstaging includes the use of a variety of treatments, such as transarterial chemoembolization, percutaneous or surgical radiofrequency ablation, selective internal radiation therapy with microspheres, ethanol ablation, and even resection. The problem is that the definition of what constitutes downstaging needs to be standardized, as pointed out in a conference regarding liver allocation, and more important, the success of downstaging needs to be critically analyzed.³¹ In a recent review of over 700 patients, it was concluded that patients who are downstaged with the methods mentioned above to within the Milan criteria (that is, a single lesion <5 cm or more than 3 lesions with none being >3 cm and without any extrahepatic disease) can have 3- and 5-year survivals that are comparable with those achieved in patients that did not require downstaging prior to the transplant.³² These findings mean that downstaging should at least be considered for patients with relatively advanced disease at presentation, so that a curative treatment may be applied. Additionally, given these results, patients that have been successfully downstaged should be transplanted with the same priority as those initially staged within the criteria. More important, though, it shows the significance of

downstaging as a way to determine tumor biology, as the patients that do not have favorable tumor biology are not likely to have successful downstaging. This allows us to possibly identify those patients with HCC that are more likely to respond to the various treatment efforts, and with whom a more aggressive approach should be undertaken.

Technologic innovations

Although there are a great number of different devices for hepatectomy in the market out there, the gold standard remains the use of the clamp-crush technique.³³ This may be along the lines of the saying that “the more things change, the more they remain the same.” However, there have been technologic innovations that can change the future landscape, as can be seen with the use of the hepatic navigation systems—an example of image-guided surgery.

There is an ongoing discussion regarding the benefits of anatomic versus nonanatomic resection. In the case of the former, the resection plane follows the segmental anatomy; whereas in the latter, the goal is to excise the tumor with negative margins. The Japanese school of thought and Makuuchi were originally in favor of the anatomic resection, based on the assumption that HCC will metastasize through the portal venous system, and thus any type of resection that would include the portal flow to the segment involved would lead to better oncologic results.^{34,35} The existence of chronic liver disease, including cirrhosis in many cases, has given support to the argument in favor of nonanatomic resection, as it leads to a bigger hepatic remnant without a difference in the overall survival.^{36,37} As appealing as it may sound, nonanatomic resection represents a challenging technique of increased difficulty. One of the solutions has been the use of virtual resection planning as a way of evaluating hepatectomy strategies suitable for the specific patient.^{38–41} A bi- or, preferably, tri-phasic CT is performed, and all the data (including the liver with the tumor and the intrahepatic vessels) are extracted, and an individualized 3-dimensional model results that is specific for the patient in question. This allows the surgical team to identify the exact blood supply to the tumor, as well as the nearby structures that could affect the resection safety margins, in addition to allowing an estimation of the volume of the hepatic remnant for the different resection strategies. Moreover, with the use of an infrared optical tracking system and a navigation

computer unit, it is possible to have this information available in real time during the procedure and thus make the necessary changes during the course of the surgery.⁴² Such a system represents a technologic innovation that can lead to hepatectomies with improved planning and increased safety.

Closely related to the issue of anatomic versus nonanatomic resection, and of being able to target a lesion, is the question of surgical resection margins necessary for HCC. Unfortunately, there is no universal agreement on what the resection margin in hepatectomy should be in order to be considered curative. In a randomized controlled trial comparing the 1-cm versus the 2-cm resection margins in patients with solitary HCC tumors without macrovascular invasion and early (Child A) stage cirrhosis, the authors reported decreased HCC recurrence and improved survival in the wider (2 cm) resection margin group.⁴³ However, this was thought to be more the result of strict patient selection (given the combination of the single lesion and the lack of macrovascular invasion) rather than an argument in favor of the wider margin. There is an increasing number of proponents of the fact that 1 cm or even any kind of margin may be enough, if we consider that the margin that the pathologist sees is not necessarily the actual margin, given that there may be a zone of necrosis, coagulation, or cauterization in the resection of the tumor.

The strategy of downstaging a tumor, or even the strategy of bridging a patient to a liver transplantation by maintaining the disease stable in the time period between the diagnosis and when a hepatic graft becomes available, brings us to the topic of locoregional therapies. They include a variety of therapies that can be applied surgically or percutaneously, depending on the tumor's location and the overall well-being of the patient. Given the limited scope of this article, these therapies will be mentioned and placed into the right context, but we will not go into detail. Specifically, one category is that of image-guided tumor ablation therapies, which includes chemical ablation (mainly with the percutaneous ethanol injection), and thermal ablation, which can be either hyperthermic, such as radiofrequency ablation (RFA), microwave ablation (MWA) and laser ablation, or cryoablation.^{44–48} Treatment with percutaneous alcohol injection involves several sessions under the guidance of ultrasound, and although there are no randomized controlled trials, it has been shown to improve the natural history of HCC.⁴⁴ Radiofrequency ablation, by causing thermal injury to the tissue through

electromagnetic energy deposition, has been shown to offer a survival advantage either alone or in combination with resection.⁴⁵ What is becoming increasingly interesting are the findings that RFA may actually have similar effect to resection as a first-line treatment in patients with early-stage cirrhosis and single lesions <5 cm.⁴⁹ Although there are limitations to these studies, the fact remains that the role of RFA may be more widespread than it was initially thought. Microwave ablation has the advantage of using electromagnetic methods and achieving much higher and much more focused energy dispersal; together with laser ablation, they represent methods that need to be closely studied, as their technology continues to evolve.^{46,47} Cryoablation is based on the application of a cryoprobe, which is cooled with liquid nitrogen, and an ice ball is created at the site of the HCC lesion.⁴⁸ The technique does have its limitations, in terms of complications with the cryoshock, and is still being developed.

Another method of locoregional treatment is based on embolization of the tumor, with the possible additional intravascular delivery of a variety of therapeutic agents. What makes chemoembolization an appealing method in the case of HCC, is the significant angiogenesis that is seen as part of HCC growth within the liver. Through this technique, it is possible to simply embolize an HCC lesion with sponge particles, so that the viable tumor is decreased and it becomes more amenable to resection. Additionally, chemotherapeutic agents, such as doxorubicin and cisplatin, can be delivered to control or decrease the size of the lesion(s). Chemoembolization has been shown to benefit patients who are too advanced for curative, surgical procedures, as it can increase overall survival.⁵⁰ It does have limitations, such as in the case of advanced liver disease or portal vein thrombosis, something which many interventional radiologists would consider a contraindication. One option to minimize any systemic effects has been the use of drug-eluting beads that sequester doxorubicin and release it in a controlled manner.⁵¹ A closely related alternative has been the use of Yttrium-90 microsphere embolization through the hepatic artery, as a method of radioembolization, which has shown remarkable results, even in advanced cases such as those with portal vein thrombosis.⁵²

Finally, newer methods of locoregional treatment are being developed and tested, including the irreversible electroporation, which is a technique that increases membrane permeability by changing

the transmembrane potential. Its advantage is that it can deliver very high amounts of energy with high speed, making it faster than the ablation methods, as well as safer; because it is not thermal ablation, it can be used for lesions close to blood vessels.⁵³ Overall, we have seen that there exist a multitude of locoregional treatments, each based on different principles and each having advantages and disadvantages. It is of paramount importance that the hepatobiliary surgeon understands how the different methods function and what they can offer, so they can be incorporated into the treatment armamentarium appropriately. Most of these methods are not curative by themselves; however, they may prove to be so in combination with surgery or transplantation. Furthermore, they do have a role as downstaging or bridging therapies, and it is thus very important to follow their evolution and development closely, so they can be used to the maximum interest of our patients.

Orthotopic liver transplantation and HCC

Liver resection and OLT should not be considered as competing when it comes to surgical treatments for HCC. The reason is that very frequently a patient may undergo a liver resection first, but in the case of recurrence or hepatic insufficiency the question of OLT comes into play. Additionally, in cases where the HCC coexists with cirrhosis of significant severity, then the option of OLT should be examined first. Either way, liver resection and OLT represent different parts of the same continuum, with each one having its advantages and disadvantages. The advantage of OLT is that it is possible to address the HCC and the underlying liver disease at the same time. The main disadvantage is the limited supply of hepatic grafts, which is also the reason for the establishment of criteria for liver transplantation for HCC. The most widely accepted prognostic factors for OLT for HCC are based on the Milan criteria, which have to do with the number and size of the lesion(s) and can lead to 5-year survival of approximately 70%.^{54,55} Given the technical success of OLT and the increasing number of patients with HCC, there has been the argument that the Milan criteria may be too restrictive, and that incrementally increasing the size of the lesions on an individual or a combined basis could potentially lead to comparable results, something which was seen with the University of California-San Francisco (UCSF) criteria.⁵⁶ In a retrospective, multicenter analysis of 1112 patients exceeding Milan criteria, based on the

posttransplant pathology review, it was seen that it was possible to achieve 5-year survival of 72%, if there was no microvascular invasion and the patients fell within the up-to-seven criteria (HCC with 7 as the sum of the size of the largest tumor and the number of tumors).⁵⁶ Essentially, this study was another step in the direction of needing to move away from strict criteria and attempting to identify the individual characteristics of the tumor, which will eventually dictate the result of the transplant. A well-established obstacle toward identifying biological features of individual tumors is that only obtained at the explant pathology, especially information regarding microvascular invasion. Further efforts along the same lines have helped the transplant community understand that we are essentially dealing with what some are calling the “metroticket” theory, whereby the further you go (the more you expand the criteria), the higher the price you have to pay (decreased survival or increased recurrence).⁵⁷ The conclusion is that we are dealing with a choice of what the medical community, and potentially society as a whole, considers as acceptable survival expectation for offering a liver graft to a patient with HCC.

Another strategy to increase the number of patients with HCC eligible for treatment through OLT has been the use of living donor liver transplantation (LDLT). Apart from an opportunity to deal with the problem of the long waiting list, LDLT also represents an opportunity in some cases for a more aggressive approach in dealing with patients with tumors that may be outside the Milan or UCSF criteria. Results have been encouraging, as seen in some of the bigger studies from Japan, where with more than half of the patients outside the Milan criteria, they were able to achieve 1- and 3-year survival of 78% and 69%, respectively.⁵⁸ It has even been suggested that survival for HCC patients may be improved after LDLT compared with OLT from deceased donors.⁵⁹ Despite these notes of encouragement, there remains significant concern, given that this is one of the few, if not the only, surgical procedure where a person undergoes a surgery with significant risk without any benefit to their health. Also, regarding the question of being more aggressive with LDLT for patients with HCC, we still have the issue of what happens should a hepatic graft primary nonfunction be encountered; that is, would that patient go on the waiting list (and possibly with priority given the severity of their medical status) for a deceased donor, or would they be excluded given that they were transplanted with

HCC outside the criteria. All these represent difficult questions, which require a lot of thought before answering.

Conclusions

We have reviewed 4 areas (staging and biologic behavior of the disease, how to increase resectability, technologic innovations, and liver transplantation) that represent some of the more important current and future challenges in the surgical management of HCC. This list, although by no means exhaustive, is indicative of the wide spectrum of issues involved in dealing with HCC. In order to be successful in this effort, the surgeon needs to be well-versed on a variety of different fronts and a member of a multidisciplinary team.

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