Chapter 5

The Role of Surgery in the Treatment of Hepatocellular Carcinoma

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1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer world-wide with approximately 700,000 new cases a year, with increasing numbers in Europe and the United States [1]. The various risk factors are reflected in the worldwide heterogeneous incidence. The majority of cases of HCC develop in eastern Asia and sub-Saharan Africa due to chronic infection with hepatitis B virus (HBV), as well as aflatoxin. In other parts of the world such as Northern America, Europe and Japan, the prevailing risk factor is chronic infection with hepatitis C virus (HCV) and alcohol use [2]. Additional or synergistic factors include non-alcoholic steatohepatitis (NASH), diabetes, obesity and tobacco, with their high prevalence in Northern America offering a partial explanation for the continuously increasing incidence of HCC [3-6].

HCC develops in cirrhotic livers in 80% of cases, as cirrhosis is one of the strongest risk factors given its role as a preneoplastic condition [7]. The mechanism itself is not fully known, although it may be secondary to the disorderly architectural changes seen in the hepatic parenchyma of the cirrhotic liver providing a signal for malignant transformation. Additionally, there could be a role for DNA damage caused by viral integration, as incidence of HCC increases with viral load and duration of infection, thus raising the possibility of a cumulative effect of long-term viral damage [8-9].

There has been major progress in understanding the nature of the disease, as well as the available therapies. Although the full range of treatment options has increased over time, especially with the advent of new surgical and molecular technologies, the mainstay of treatment remains surgery, as the only truly therapeutic option. This chapter will discuss the evaluation of the patient with HCC, the two main surgical treatments, liver resection and orthotopic liver transplantation (OLT), as well as future prospects which include the molecular classification of HCC and the efforts for targeted molecular therapies, which in turn will have a great impact on any therapeutic decision.

2. Evaluation of patients with hepatocellular carcinoma

In order for surgical treatment for HCC to be successful, patients need to be chosen very carefully. It is essential that the evaluation, selection and treatment are performed by multi-disciplinary teams that include hepatologists, surgeons, oncologists, radiologists, pathologists and anesthesiologists. The reason is that we have to remember that we are dealing with more than one problem in the same setting. Specifically, the patient's HCC needs to be addressed, but it has to be done in the setting of the possible cirrhosis. The degree that the patient's liver function is affected can have a direct impact on several other organ systems (cardiopulmonary, renal) and thus directly influence any therapeutic decisions. It is interesting that, in contrast to several other cancers, there are not many randomized controlled trials to compare the treatments seen as curative for HCC, something which underscores the need for these patients to be followed in protocols whenever possible, so that evidence-based decisions can be made.

The first question that has to answered is whether the patient is an operative candidate, meaning whether the patient is in a position to undergo a major surgery from the standpoint of his overall health. It is essential that this evaluation is performed by physicians who are intimately aware of the challenges of liver resection or transplantation. For example, the anesthesiologist has to be aware that this will be an operation with potential significant blood loss and periods of hypotension, all of which will stress the cardiovascular system. This should help determine the kind of preoperative testing that is needed, although there is to-date no universally agreed upon preoperative protocol for patients undergoing liver resection. The importance of this can be seen even more clearly if we consider that given the improvements in surveillance and surgical technique and the general ageing of the population, older patients belonging to a higher risk group are being increasingly evaluated for liver surgery. Once the question of the patient as an operative candidate has been answered satisfactorily, the next one is whether the HCC is resectable. The answer to this question depends on identifying the stage of the disease, as well as the hepatic reserve of the patient.

2.1. Staging of patients with hepatocellular carcinoma

Regarding the stage, there is a lack of a common language as there is no consensus on a universal staging system. There are different ones, each one taking slightly different aspects of the disease into consideration. Some depend on clinical and radiological findings prior to the treatment, whereas others are based on the histopathological findings. Ideally, clinically-applicable staging for HCC should assess the tumor stage, the underlying liver function and the patient's biological status. Some of the staging systems, such as The American Joint Committee on Cancer/Union Internationale Contre le Cancer Tumor-Node-Metastasis staging system (AJCC/UICC TNM) stratifying patients into prognostic groups, are best suited to only patients undergoing resection or transplantation, without taking into consideration the underlying liver disease [10]. In an effort to consider tumor features and hepatic function, the Okuda system and the Cancer of the Liver Italian Program (CLIP) classifications were proposed [11-12]. Both of them have the ability to identify end stage disease but are not as accurate with early stage disease. A step towards solving this problem has been the Japan

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Integrated Staging score, which combines the Child-Turcotte-Pugh (CTP) classification with the simplified TNM system by the Liver Cancer Study Group of Japan (LCSGJ) [13].

The most widely accepted system appears to be the Barcelona Clinic Liver Cancer (BCLC) system, which was introduced in 1999 as an attempt to improve on the Okuda system, so as to include the functional aspect of the disease. It was developed based on a combination of data from a variety of studies looking into different types of treatment for different stages of the disease [14-16]. The BCLC takes into account the total cancer load, the stage of the cirrhosis and the patient's functional status, in an effort to determine the type of treatment necessary and the expected survival (Figure 1). It is the staging system most widely (but not universally) accepted, as it has been externally validated and it offers a pathway between staging and the different treatment modalities with an estimation of life expectancy [17]. It provides suggested treatments for the different stages of the disease, including early stage HCC where the aim is a cure, as opposed to advanced HCC where palliative treatments are proposed. In addition to providing proper patient care, universally-accepted staging for HCC is critical in allowing the comparison between results from different studies in order to draw the appropriate conclusions. A system such as the BCLC, which is a clinical system with predictive abilities, can offer a solid platform for the initial staging. Other systems, such as the simplified TNM, which includes pathological findings such as microvascular invasion, can be of more value in those patients undergoing resection or OLT.

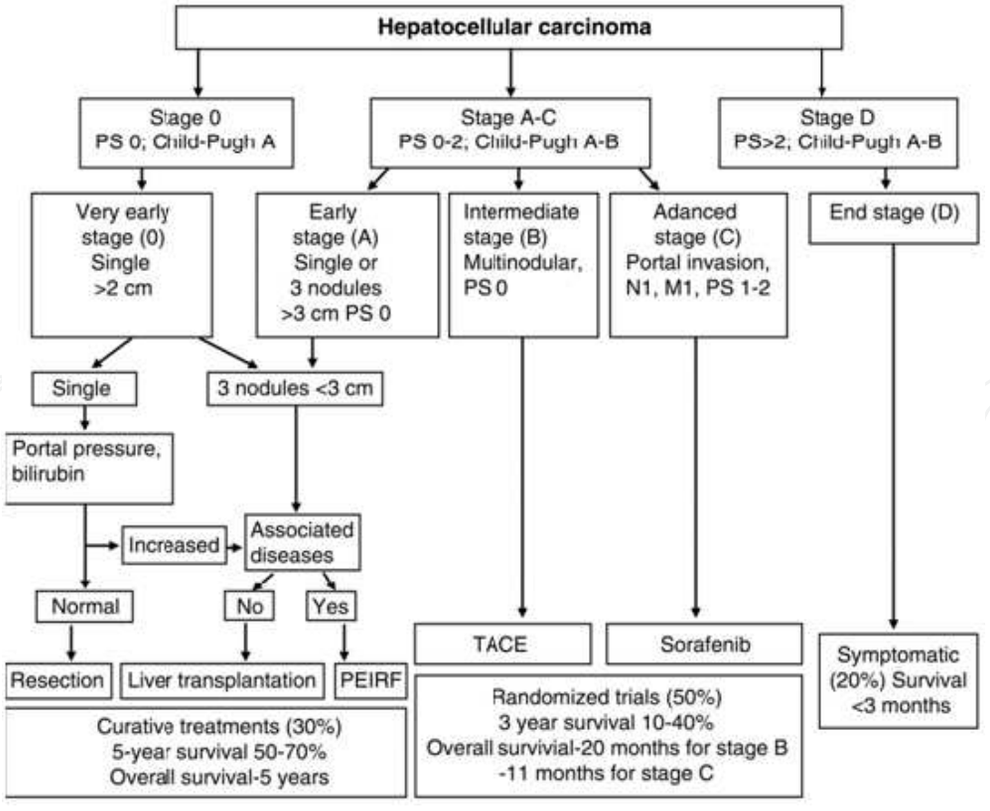

Figure 1.

2.2. Evaluation of hepatic reserve of patients with hepatocellular carcinoma

As far as evaluating the hepatic reserve of the patient is concerned, that is a determination of both quantity and quality. This is a major change from the past when there were multiple exclusion criteria, as the only ones that have been consistently validated over time are the postoperative remnant liver volume and hepatic function [18-20]. It has been shown that if 3 or more hepatic segments are left behind after a resection, or an adequate hepatic remnant, which is 25% for a normal liver and 40% for a cirrhotic one, then postoperative liver dysfunction can be avoided [21-22]. This means that it is essential to be able to accurately estimate the liver remnant and the future remaining liver volume preoperatively, especially in the case of extended resections. The most reliable way to do this has been CT volumetry, which with the advent of the Digital Imaging and Communications in Medicine (DICOM) standard has enabled volumetry to be performed even by the surgeon on a personal computer. Quality can be assessed either directly (liver biopsy) or indirectly, through assessment of the synthetic function of the liver (INR, platelets, albumin) or other marks of portal hypertension and cirrhosis, such as esophagogastroduodenoscopy (EGD) looking for varices. The underlying chronic liver disease, including its duration and whether the patient has received any treatment, are also important pieces of information.

By fully evaluating the patient with HCC, one can proceed more safely into determining whether the patient is a candidate for surgical treatment and which one: resection versus transplantation. Frequently, it may be necessary for the patient to be evaluated for both, as a patient undergoing a liver resection could show signs of hepatic failure postoperatively, leading to a discussion of whether transplantation is an option. It is wise for these decisions to be made beforehand, rather than during emotionally-charged times.

3. Hepatectomy

The first question one has to consider when discussing the issue of hepatic resection for HCC is the presence or not of cirrhosis. In non-cirrhotic patients, hepatic resection represents the preferred treatment, as the lack of cirrhosis means that the patient can tolerate even an extended resection, and the non-cirrhotic liver will allow future re-resection, although it has a lower chance of de novo recurrence. Unfortunately, these patients without cirrhosis represent only 5% of cases in the West [23]. Even so, in these patients without cirrhosis, surgical resection for HCC can lead to 3-year survival of 46-76% and 5-year survivals of 30-50%, depending on the selection criteria and on whether fibrolamellar HCC cases are included in the study [24-26]. A high recurrence rate at 5 years of around 60% remains, even after potentially curative resections, possibly owing to intrahepatic metastases rather than existing disease, as the effect of the underlying chronic liver disease and the cirrhosis is not present [27].

In patients with cirrhosis, using proper selection criteria to avoid postoperative hepatic failure is critical. That set of criteria was originally based on the Child-Pugh classification, which however was not shown to have a consistent predictive value, as patients may show signs of hepatic dysfunction even at a stage of Child-Pugh A, thus making a resection

a high-risk one [28]. The best candidates for liver resection, and those who could achieve 5-year survivals of up to 70%, are those patients with single lesion, asymptomatic HCC, and most importantly with preserved liver function [29-31]. The definition of preserved liver function includes the absence of clinically significant portal hypertension (hepatic vein wedge pressure difference less than 10mmHg, absence of varices or splenomegaly, and platelets over 100,000/mm^3) and normal bilirubin values [32]. In patients with significant portal hypertension, 5-year survival after resection goes down to 50%, whereas in those with combined portal hypertension and increased bilirubin levels it can be as low as 25% [33]. In order to predict the risk of postoperative hepatic insufficiency other groups have used the Model for End-stage Liver Disease (MELD) score, which is based on the values of the patient's creatinine, bilirubin and prothrombin time. Several studies have shown that when the MELD score is 9 or less, then hepatic resection can be safe with almost minimal chances of postoperative patient destabilization [33-35].

The preference for patients with a single lesion has to do with the fact that in most cases multifocal HCC is associated with decreased survival and increased recurrence, potentially as an indication of already existing intrahepatic metastases. Although not prohibitive for resection, the presence of multiple lesions should alert the surgeon to the possibility of using treatments such as radiofrequency ablation and chemoembolization in combination with resection to obtain optimal results. Similar to multifocality, an increased tumor size is not necessarily prohibitive, but can serve as an indication of possible vascular invasion, which can in turn negatively affect the prognosis. When all of this is considered, the percentage of patients that can undergo hepatic resection under ideal conditions is less than 10%. However, even in this group of patients with cirrhosis, it is possible to achieve moderate long-term results [36-38].

3.1. Considerations in liver resection

When considering liver resection for HCC apart from the main question of the presence or absence of cirrhosis, there are other key issues to be addressed, such as ways to increase resectability, the differences between anatomic and non-anatomic resection and the use of laparoscopic surgery among others.

3.1.1. The role of portal vein embolization

In an effort to treat large HCC with hepatic resection or in those patients with inadequate liver remnant, there are certain preoperative manoeuvres that can help increase resectability in these challenging patients. Preoperative portal vein embolization (PVE) was introduced in 1986 by Kinoshita to prevent postoperative hepatic insufficiency, whereas Makuuchi had first introduced the concept to clinical practice in 1982 for the treatment of hepatic cholangiocarcinoma [39-40]. The main principle is to occlude the portal venous flow to the side of the tumor, and cause ipsilateral atrophy and, more importantly, contralateral hypertrophy of the part of the liver that will be the future remnant after the resection. This can lead to an increase in the future remnant by about 20-40% within 4-6 weeks, thus potentially increasing the pool of candidates for resection [41-43]. Although there are no absolute contraindications, especially as experience with the procedure continues to grow,

there are some relative ones, including uncorrectable coagulopathy, tumor invasion of the portal vein, biliary dilatation and renal failure. Bilobar disease used to be a contraindication, however in light of the increased use of the two-stage hepatectomy, PVE can play a significant role in these patients [42,44]. Although there are two methods to access the portal vein for PVE, the transileocolic and the percutaneous transhepatic one, with both being equally effective, the percutaneous procedure has the distinct advantage of avoiding a minilaparotomy and general anesthesia. Regarding the choice of embolic agents, there is a great variety with similar results. However, since it is not an exact science how much embolic material or what size particles are needed to cause a specific amount of hypertrophy and regeneration, we need to understand that this procedure is very much operator-dependent. Certain principles need to be closely adhered to, such as embolizing till stasis is achieved, and also avoiding reflux of the embolic material into the veins that will supply the future liver remnant.

There are some remaining concerns regarding PVE, such as whether PVE may stimulate the growth of hepatic tumor (of more interest in the case of hepatic metastases from colorectal or other cancers), or whether it is a safe procedure in patients with high-grade varices. The difficulty in answering these questions is the fact that we lack an understanding of the mechanism involved in the contralateral hypertrophy caused by the PVE. It is probably a combination of hepatic and extrahepatic factors, including cytokines (such as IL-6), growth factors (such as hepatocyte growth factor) and nutrient factors (insulin and glucagon), although the details are not yet clear [45]. Either way, PVE provides the surgical team with an important tool that if properly applied can lead to increased resectability of HCC.

3.1.2. Anatomic versus non-anatomic hepatic resection

Hepatic resection for malignant tumors can be anatomic or nonanatomic. The anatomic approach involves a resection of liver segments based on the segmental anatomy, whereas the nonanatomical approach involves a resection of the tumor with negative margins. The main argument in favour of the anatomic resection was made by Makuuchi and the Japanese school of thought, where based on the fact that HCC tends to metastasize via the portal venous system, it is believed that removing the tumor along the lines of hepatic segments, which would include the portal flow to the tumor, is the more oncologically sound approach [46-47]. Using a nationwide Japanese database of 72,744 patients to compare the outcome of anatomic versus nonanatomic resection for HCC, it was shown that there was no difference in overall survival, although with anatomic resection there was an improved disease-free survival [48]. The beneficial effect of anatomic resection was most prominent for HCC lesions 2 to 5 cm, something which was explained by the fact that in smaller tumors there is very little chance of vascular invasion, whereas in bigger ones the high probability of vascular invasion and satellite lesions negates any advantage of an anatomic resection. Despite this, the extent of the hepatectomy should be primarily dictated by the extent of the existing chronic liver disease and the future liver remnant.

This type of argument has given impetus to the use of nonanatomic resection for HCC, as in the vast majority of cases the HCC occurs in the background of cirrhosis. Even so, the question

remains of what the proper margin for the nonanatomic resection is. Specifically, there is an ongoing debate as to whether a margin of 1cm or more is necessary to obtain disease-free survival, or whether less than 1cm is sufficient [49-51]. A prospective, randomized trial comparing narrow (1cm) to wide (2cm) resection margins identified a significant 5-year survival benefit (75% versus 49%) for the wide margin group, especially in patients with small HCC of 2cm or less [52]. Even so, a report by the Japan Society of Hepatology in 2010 states that "it is acceptable to resect a tumor with a minimum width so as to avoid exposing the tumor during hepatectomy for HCC" [53].

3.1.3. Laparoscopic liver resection

Although the first laparoscopic liver resection (LLR) was performed in 1992 by Gagner, it has been somewhat of an uphill struggle because of several reasons [54]. Potential difficulties of LLR include a significant learning curve, the perceived difficulty in controlling hepatic bleeding should it occur, the lack of tactile sense which could affect the margins obtained and thus the oncological result of the procedure, the fear of port site metastases and that of gas embolism. To all of these we should add the lack of randomized trials with LLR. Improvements in hepatic surgery, as well as in laparoscopic surgery, advances in the laparoscopic instruments used, and patient interest in minimally invasive procedures, have all led to a significant increase in the number and type of LLRs. There has also been increased use of LLRs for hepatic malignancies, as currently more than half of all LLRs are for primary or metastatic hepatic malignancies, including anatomic lobectomies and liver resections in cirrhotic patients [55-58]. The key factor is surgeon experience and the learning curve, as in one paper it was shown that the learning curve for minor laparoscopic hepatectomy could be overcome with 60 cases [59]. The surgeon needs to be a liver surgeon with knowledge of hepatic anatomy, as well as someone with experience in advanced laparoscopic surgery, so that issues such as control of vascular or biliary structures can be dealt with laparoscopically. Additionally, experience with laparoscopic ultrasound is mandatory, as it counterbalances the lack of tactile sense. Common sense dictates that at least the earliest laparoscopic procedures performed by a surgical team should include smaller, peripheral lesions away from major vascular structures or the hilum that can be approached with a laparoscopic wedge or segmental procedure.

In the case of HCC, several series have shown a good long-term outcome without jeopardizing patient safety [60-62]. Some of the findings in these studies included decreased blood loss and transfusion requirements for LLR, as well as a shorter length of stay. Although the latter may come as no surprise given the minimally invasive nature of the procedure, the former could be potentially attributed to new and improved coagulation and transection devices used in LLR. Another advantage of LLR is the possible decreased risk of hepatic function destabilization, if we consider that most of these patients have cirrhosis. It is believed that the lack of the big abdominal incisions, can cause less of an effect on the portal pressure, thus decreasing the risk of postoperative hepatic decompensation [63-64]. The result of the decreased biological and surgical stress for the patient could also be part of the reason why it was shown that prior

LLR for HCC facilitated salvage liver transplantation with improved results compared to prior open liver resection [65].

3.1.4. HCC recurrence after resection

HCC recurrence after hepatic resection is a significant concern with reported rates between 60-70% at 5 years [66-68]. The challenge lies in deciding what the best treatment for these patients is. The options include a second resection versus radiofrequency ablation versus salvage liver transplantation. Evaluating radiofrequency ablation has not been easy as there are significant variations in the inclusion criteria used in the various studies. Regarding OLT, an analysis of the UNOS database by Pelletier et al. reported a 61% 5-year intention to treat survival of patients with tumors within Milan criteria [69]. However, there have been studies advocating the use of a second resection in properly selected patients. In the largest study in the Western world a 5-year 67% overall survival was reported from a second resection after HCC recurrence, with the two main risk factors being gross vascular invasion and time to recurrence from primary resection less than a year [70]. It should be noted though that when these strict criteria were used, only 15% of patients with recurrence were candidates for a second resection.

3.1.5. Liver resection as a bridge to OLT

The issue of HCC recurrence raises an important question. When discussing the different surgical treatments of HCC, it is imperative to stress the fact that liver resection and OLT are not necessarily competitive surgical options, but can very frequently be seen as complimentary. Specifically, the cirrhotic patient who undergoes a hepatectomy for a HCC, no matter how stable the liver function is, certainly runs the risk of peri- or post-operative liver failure, thus necessitating an urgent evaluation and referral for OLT. The implication here is that patients with HCC and cirrhosis should be evaluated for both liver resection and OLT and preferably be treated at a center where both options are available.

4. Orthotopic liver transplantation for HCC

Patients suffering from cirrhosis and HCC that are not candidates for resection, either because of the degree of liver disease or the location or anatomy of the tumor, are best treated by OLT. The main advantage is that OLT provides a solution for both the cirrhosis and the HCC. The problem arises from the fact that there is a limited organ supply, and for that reason there have been criteria established for patients to enter the waiting list. The most frequently used ones are the Milan criteria (single lesion less or equal to 5 cm in size or three or no more than three lesions, none of which are over 3cm in size), which can lead to 5-year survival of 70% [9]. There has been an effort to expand these criteria, as it has been shown that moderate expansion in terms of number and/or size of the lesions can lead to comparable survival.

This chapter will analyze the following issues having to do with OLT and HCC: a) results for OLT for HCC and criteria used to prioritize these patients, b) the practice of bridging therapies

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to OLT and downstaging prior to OLT, and c) the role of living donor liver transplantation (LDLT) for OLT.

4.1. Results and criteria for OLT for HCC

As mentioned above the most consistent prognostic factors regarding OLT for HCC are derived from the characteristics originating from the Milan criteria having to do with the size and number of the lesions, in addition to no macrovascular involvement and no extrahepatic metastatic disease to lymph nodes, lungs, bones, or other abdominal organs. These criteria can lead to 5-year survival of around 70% and recurrence-free survival of 70-80% [70-71]. In properly selected patients, it is possible to achieve even long-term results that are more than satisfactory with 9-year survival of 52% [72]. Getting to this point however has been challenging, as there is a continuous need to reevaluate the listing and priority criteria for OLT for HCC.

Originally, HCC was considered a contraindication for OLT given the dismal patient survival rates that were the result of patients being transplanted at a very late stage of their cancer, as the technique was still considered experimental. The combined work of Bismuth in 1993 and the subsequent Milan criteria by Mazzaferro showed that if patients were carefully chosen, so that the lesions were within a certain number and size, then it was possible to achieve these excellent results with OLT for HCC [70, 73]. Recently, however, several groups have argued that the Milan criteria are too restrictive and that more patients with HCC could benefit from OLT. The strongest argument along these lines is based on the University of California San Francisco (UCSF) criteria (single HCC lesion up to 6.5cm diameter or up to three lesions, none larger than 4.5cm, with a cumulative diameter of 8cm) [74]. Another retrospective study with the largest number of patients outside the Milan criteria has shown encouraging outcomes by using the "up-to-seven" rule [75]. This approach uses the sum of the combination of size and number covariates equal to seven or less. Although it appears as a strong proposal to expand the existing criteria, it does have the disadvantage of being based on post-transplant pathology. All of this has led many to discuss the "metroticket" theory, which is based on the belief that the further you go (the more you expand the existing criteria), the higher is the price you will be forced to pay (decreased survival and increased recurrence) [76]. In the United States, where the MELD score is used for listing, patients within the Milan criteria receive 22 MELD exception points for transplantation priority [77]. Despite an additional 10% increase in MELD every 3 months, patients may end up waiting 6 months to a year, depending on the region that they are [77].

4.2. Bridging therapy to OLT for HCC

The fact that, despite receiving extra priority points on the waiting list, patients with HCC may still have to wait significantly and risk falling outside the Milan criteria, makes the issue of bridging therapy all the more important. Bridging therapy is mainly aimed towards patients that are already within Milan criteria and thus eligible for OLT, and for whom the goal is to avoid tumor progression while on the waiting list. Although it is hard to clarify the usefulness

of bridging therapy for patients with HCC, mainly because of the retrospective nature of most studies on the topic, it has been shown that the drop-out rate while on the waiting list increases as waiting time progresses, especially in the case of HCC [78]. Based on the estimates that have formed the basis of the UNOS MELD score exception policy, it is suggested to use bridging therapies for T2 patients, even if the estimated waiting time is less than 3 months [79].

Regarding the question of which therapy is best for bridging, the most promising therapy appears to be radiofrequency ablation, as several studies have shown decreased drop-out in radiofrequency ablation pretreated patients with a single HCC nodule [80-81]. Additionally, there may be a role for transarterial chemoembolization (TACE) for patients with lesions larger than 3cm or with a multinodular pattern, although this has not been verified in prospective studies. Another possibility, which is currently under investigation, is the use of transarterial radioembolization with Uttrium-90 microspheres, with promising results to this point [82-83].

4.3. Downstaging therapy for HCC prior to OLT

Downstaging refers to the effort made in patients that find themselves outside the Milan or UCSF criteria for transplantability, to decrease their tumor burden to the extent that they fall within these criteria again. This way, these patients become candidates for OLT. Additionally, it is thought that the response to downstaging and the maintenance of this response represent a surrogate marker of the aggressiveness of the tumor, which in itself could help guide any decisions regarding the transplantability of a patient [84]. As to which the best method for downstaging is, TACE appears to have the advantage for single treatment, especially for multifocal tumors [84]. Even so, the combination of TACE, radiofrequency ablation and resection seems to be an even more effective method of downstaging compared to TACE alone (70% success versus 40%) [83, 85].

4.4. The role of living donor liver transplantation in the management of HCC

For many, LDLT represents a possible solution to the organ shortage problem and the long waiting list; for others it presents an opportunity for an aggressive approach in dealing with HCC patients whose tumors are outside the accepted criteria (such as the Milan and UCSF ones), if a suitable living donor exists. Currently in the US, LDLT represents about 5% of all liver transplantations. Despite the fact that the experience with LDLT is still being accumulated, there appears to be significant optimism. In one of the bigger studies from Japan with 316 patients undergoing LDLT for HCC, one- and three-year survivals were 78% and 69% respectively, whereas recurrence-free one- and three-year survivals were 73% and 65% [86]. Although these results may not seem as impressive at first, it should be noted that 54% of these patients were outside the Milan criteria, thus representing a higher risk group. Some studies have shown improved survival for patients undergoing LDLT compared to those undergoing OLT from deceased donors, with 1-year survival of 86% for LDLT versus 71% for deceased donor recipients [87]. Despite these encouraging results, there remains a lot of concern. The main reason is the consideration that the health of the living donor is placed at risk, as living donors are in the unique situation of undergoing a major surgical procedure without any health benefit to themselves. Additionally, regarding the argument of expanding HCC criteria

for patients undergoing LDLT, since they have their own living donor, the question remains of what should happen if these recipients suffer hepatic dysfunction or nonfunction of the liver graft. That is, should they be listed in the deceased donor waiting list, something which would not have been possible before, given the size or number of their lesions. The answer at this point appears in most cases to be "no" and thus these are all considerations that should be carefully addressed by the surgical and medical teams before proceeding with a LDLT for HCC. Finally, as it has been seen in one of the bigger, multicenter trials in the US, the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL), although the survival results between recipients of deceased donor and living donor transplantation are similar, there appears to be a higher chance of recurrence after the LDLT of 29% versus 0%, despite the much shorter waiting time (160 days for LDLT versus 469 days for deceased donor OLT) [88]. However, this could also be because of the shorter waiting time, as some would argue that by being able to proceed to transplantation quickly, one loses the "opportunity" to evaluate the biological behavior of the HCC.

5. Future challenges

Given the significant developments and progress in surgical technique, the biggest challenge in the treatment of HCC is identifying the biological behavior of a given tumor, so that a patient-tailored, or rather a tumor-targeted, treatment can be applied. To do this, it is necessary to identify those factors, other than tumor size and number, that determine tumor aggressiveness. Several studies have identified a variety of parameters, such as the response to chemoembolization, the presence of microvascular invasion, the degree of differentiation and the combination of total tumor volume (TTV) together with AFP as surrogate markers for the tumor's biological behavior [89-93]. Regarding the latter, in an overview of the Scientific Registry of Transplant Recipients data from March 2002 to January 2008, it was shown that AFP>400 ng/ml or TTV>115 cm^3 led to a three-year survival of less than 50% [94]. Essentially, this represents a novel approach, where the issue is not necessary the number or size of the HCC lesions per se, but rather the total tumor load.

The most promising area in terms of defining the nature and behavior of HCC is that of molecular biology, with the use of genetic markers. Currently, identification of targets such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor receptor (PDGFR) has led to medications being used in clinical practice for advanced HCC, such as sorafenib and imatinib [95-98]. More importantly, the identification of microRNAs (miRNAs), which are a non-protein coding family of genes regulating gene expression, has opened a new window to the future. Specifically, they have been shown to function as oncogenes and tumor suppressor genes, making this a very useful screening tool for potential resection or liver transplantation candidates [99-100]. Several miRNA targets have been identified, with prominent among them miR-122a and miR-21, with the former being down-regulated and the latter up-regulated in HCC [101-102]. Advances in understanding the multistep process that is hepatic carcinogenesis, as well as beginning to identify the different signaling cascades involved, has provided researchers and clinicians with the opportunity to proceed with

molecular classification of HCC [103-104]. This will provide critical information in terms of assessing the biological behavior of different HCCs, which in turn can help improve the therapeutic decision-making process.

6. Conclusion

Hepatocellular carcinoma is a disease with a far-reaching effect globally. The main therapeutic treatment method remains surgery, with the two options being liver resection or orthotopic liver transplantation. This chapter has discussed patient evaluation and selection for the different therapies, the advantages and disadvantages of liver resection and transplantation (with special emphasis on the fact that they both have a role in the continuum of care for these patients), and the future challenges and opportunities provided by the molecular tools available to today's surgeon.

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