Chapter 7
Surgical Treatment for Hepatocellular Carcinoma

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Abstract The treatment of hepatocellular carcinoma (HCC) has undergone evolution and refinement over the past three decades. Changes in the understanding of HCC with respect to tumor size, number and location, underlying liver function and portal pressure, and hepatic anatomy, in combination with refinement of surgical techniques and technologies, have greatly influenced the approach to surgical management. Surgery is considered the mainstay of curative HCC treatment with resection and transplantation achieving the best outcomes in well-selected candidates (5-year survival of 60–80 %). Surgical resection of HCC, especially within the Milano/Mazzaferro criteria (i.e., solitary tumor $\leq$5 cm or up to three tumors all $\leq$3 cm) in patients with well-preserved liver function (Child-Pugh A and selectively B patients), offers the greatest chances for survival. Liver transplantation is considered the treatment of choice for patients with compromised liver function (Child-Pugh B/C). The clinical parameters identified in this Chapter will be used to generate Digital Patient Models (DPMs) to facilitate diagnosis, prognosis, and treatment selection, i.e. Model Guided Therapy (MGT). The following have been identified as key issues relating to Predictive, Preventive, and Personalized Medicine (PPPM) and surgical treatment for HCC: tumor characterization, such as size, number, and vascular invasion; the patient's clinical status, particularly the presence of cirrhosis, the degree of portal hypertension, and liver functional reserve; pre-operative management, such as patient selection for resection or transplantation, choice of donor, down-staging and bridging therapies; and, surgical techniques, including techniques to minimize blood loss and to ensure an adequate liver remnant.

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L. Berliner, H. U. Lemke (eds.), *An Information Technology Framework for Predictive, Preventive and Personalised Medicine,* Advances in Predictive, Preventive and Personalised Medicine 8, DOI 10.1007/978-3-319-12166-6_7

Keywords Personalized medicine · Hepatocellular carcinoma · Staging · Treatment · Surgery · Hepatectomy · Liver Transplantation · Down-staging · Bridging Therapy

7.1 Introduction

The treatment of hepatocellular carcinoma (HCC) has undergone evolution and refinement over the past three decades. Changes in the understanding of HCC in the context of a wide variety of factors such as tumor size, number and location, underlying liver function and portal pressure, and hepatic anatomy, in combination with refinement of surgical techniques and technologies, have greatly influenced the approach to surgical management. Concerted efforts have been made to review and consolidate the worldwide experience in the management of HCC and recommendations for optimal treatment protocols, based on patient staging, have been made reflecting these findings [1–4].

Surgery is considered the mainstay of curative HCC treatment with resection and transplantation achieving the best outcomes in well-selected candidates (5-year survival of 60–80%) [3]. In general, surgical resection of HCC, especially within the Milano/Mazzaferro criteria for liver transplantation (i.e., solitary tumor ≤5 cm or up to three tumors all ≤3 cm) in patients with well-preserved underlying liver function (Child-Pugh A and selectively B patients), offers the greatest chances for survival, while liver transplantation, in patients with compromised liver function (Child-Pugh B/C), is generally considered the treatment of choice. It is important to note that these recommendations are undergoing constant reassessment and revision. The application of specific techniques, such as radiofrequency ablation (reviewed in Chaps. 8 and 9) and the practice of reclassification of patients with well-compensated liver function, have, in some reports, suggested alternative treatment protocols. These issues relating to surgical management of HCC, and which emphasize the trend toward personalized medicine in HCC, will be discussed in this Chapter.

7.1.1 Surgical Resection

Surgical resection is the optimal treatment for HCC in non-cirrhotic patients (Child-Pugh A) in that it may be curative and because of the high reserve and regenerative capacity of a non-fibrotic liver [5]. Unfortunately, in Western countries only approximately 5% of patients present with HCC without cirrhosis [6]. In Asian countries, approximately 40% of patients will have HCC without cirrhosis due to the high incidence of hepatitis B virus (HBV) infection which predisposes patients to HCC in the absence of cirrhosis [6]. However, with careful patient selection and improved surgical techniques, peri-operative mortality rates in cirrhotic patients

with HCC have been reported to be 2–3% with a 5-year survival rate of approximately 60% and blood transfusion requirements of less than 10% [3]. Selection criteria for surgical resection has previously been based on the Child-Pugh class, however surgical outcomes have been improved when independent criteria, like serum bilirubin levels and presence of portal hypertension, are used to risk stratify operative candidates [7,8]. The Barcelona Clinic Liver Cancer (BCLC) criteria stratify patients for therapy in this fashion [1–3]. Patients with normal bilirubin levels and hepatic-portal vein gradient (HVPG) < 10 mm Hg have been reported to have a 5-year survival rate of < 70%. This is in contrast to patients with hyperbilirubinemia and portal hypertension who have a < 30% 5-year survival rate [7]. Surrogates of portal hypertension include esophageal varices and splenomegaly with platelet count < 100,000/mm^3) [3].

The size and number of tumors, the presence of microsatellites, the presence of vascular invasion, and the width of resection margin have all been shown to have prognostic significance [3, 9–11]. Improved postoperative 5-year survival rates have been shown in patients with tumors < 5 cm in diameter (66% for tumors < 2 cm, compared with 52% for tumors 2–5 cm and 37% for tumors > 5 cm) and with fewer numbers of tumor nodules (73% with one tumor vs. 44% with 3 or more tumors) [11]. The major contraindication to resection of HCC is the presence of extrahepatic disease, as HCC commonly spreads to lymph nodes, lungs, and bone [12].

Vascular invasion has been shown to play a major role in tumor recurrence and it is thought that recurrence often involves spread from the primary resected tumor, rather than metachronous tumor development [4, 13]. Microvascular invasion has been shown to be a significant factor affecting prognosis after surgical resection, especially with identification of invasion of a muscular vessel wall or of invasion more than 1 cm beyond the tumor edge as the two worst risk factors for prognosis [14]. Tumor resection margin also influences recurrence rate in that wider margins (2 cm vs. 1 cm) taken on solitary tumors have been shown to both decrease recurrence and improve survival [15].

Several treatments have been studied as adjuvant therapies to reduce recurrence after resection of HCC. This includes the use of interferon, chemotherapy, preoperative chemoembolization, internal radiation with 131I-labeled lipiodol, immune therapies with activated lymphocytes with interleukin-2 and retinoids, and vitamin K. At this time, the studies have not been sufficiently large or conclusive enough to support their use to improve postoperative survival [3,16].

Pre-operative portal vein embolization (PVE) of the branches supplying the portion of the liver to be resected (with the intention of increasing the residual liver volume if a major resection is envisioned) has been studied [17]. The average increase in the future liver remnant (FLR) following PVE is 9% and 16% in cirrhotic and normal liver, respectively [17] and PVE has been used to increase the volume of the FLR in all patients who undergo trisegmentectomy [12]. PVE has also been employed in those patients with chronic liver disease who are to undergo right hemihepatectomy or when the FLR is less than 40% [12]. However, PVE is associated with a complication rate of 10–20% and the occurrence of severe portal

hypertension in 1% of cirrhotic patients [18]. The overall effectiveness of PVE in the treatment of HCC in cirrhosis has not yet been properly tested in large controlled studies [3].

7.1.2 Surgical Resection Techniques

In addition to selecting patients with preserved liver function reserve, a variety of surgical techniques may be employed to minimize blood loss, which is highly associated with patient outcomes [3]. This includes pre-resection imaging planning, use of ultrasonic dissector, intermittent Pringle maneuver, low central venous pressure maintenance, and immediate post-operative management. These strategies have led to a decrease in blood transfusion from 80 to 90% to less than 10% in two decades [19].

The implementation of anatomic resections according to the Couinaud segments has ensured a surgical approach based on sound oncologic principles, although associated with modest decrease in early recurrence [3]. As described above, anatomic resections of 2 cm margins provide better survival outcome than narrow resection margins < 1 cm. However, it is important to maintain sufficient remnant liver volume to ensure adequate function.

Finally, laparoscopic video-assisted hepatic resection is being investigated as an alternative non-invasive approach aimed at preventing liver deterioration compared to open surgery [3].

7.1.3 Liver Transplantation

Liver transplantation is a curative option for patients with HCC, especially for those with underlying cirrhosis who may be poor candidates for surgical resection. Patients with a single lesion ≤5 cm, or up to 3 lesions each ≤3 cm in diameter, who meet the United Network for Organ Sharing (UNOS) criteria and those meeting extended criteria of University of California San Francisco (UCSF) which allows for a single lesion ≤6.5 cm or up to 4 lesions with none >4.0 cm and a maximum combined tumor bulk of ≤8.0 cm have shown excellent 5-year survival rates of approximately 70% [20–22]. However, the UCSF criteria have not been adopted by UNOS for liver transplantation in patients with HCC.

Priority for transplantation is given to the patients with the earliest predicted mortality which is calculated using the Model for End-Stage Liver Disease (MELD) score [23]. Although MELD is useful prognosticating patients with many forms of chronic liver disease including cirrhosis, the MELD score alone may underestimate disease severity in patients with HCC creating a disadvantage for these patients in obtaining a liver transplant. To make the MELD system more equitable for patients with HCC, exception points are given in an effort to ensure that all patients on the

liver transplant waiting list will be transplanted in an order where patients with the earliest expected mortality are prioritized.

Currently, patients with a single lesion between 2–5 cm, or up to 3 lesions (each lesion < 3 cm), are automatically given a MELD of 22 [24]. If their calculated score is higher than 22, then the calculated score may be used. Patients who receive a MELD upgrade also receive an increase in score by 10 % at each 3 month interval after listing for liver transplantation [20]. Since the MELD system with exceptions for HCC was adopted in 2002, total number of liver transplantations performed in patients with HCC has increased nearly 6 fold. From 1997 to 2002 (pre-MELD exception) 4.6 % of all liver transplants were in patients with HCC compared to 26 % of all liver transplants performed in patients with HCC from 2002 to 2007 [25].

7.1.4 Down-staging and Bridging Therapies

Down-staging of HCC is the use of localized tumor therapy in an effort to reduce tumor size and number of nodules prior to transplantation. In some cases, transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) have been shown to successfully down-stage tumors prior to transplant [26]. Recent data has shown benefit in use of ablative therapy prior to transplantation [27]. Patients with HCC who received ablative therapy prior to transplantation were compared to those who did not receive ablative therapy and were shown to have similar 3 month and 1 year graft and patient survival; however, those who received ablative therapy had improved graft and patient survival three years after transplantation (graft survival 76 % vs 71 %, patient survival 79 % vs 75 %) [27].

One significant problem facing patients with HCC waiting for liver transplant is the risk of dropout due to the progression of disease beyond transplant criteria. By 6 months, 20 % of patients will no longer be eligible for transplant and by 1 year at least 70 % of patients with untreated HCC will have tumor growth, 20 % will develop vascular invasion, and 9 % will develop metastases [28]. Locoregional ablative therapies have served as a bridge to transplantation or as destination therapy in patients who are not originally transplant candidates. These treatments have been used to downsize tumors and prevent lesions from exceeding transplantable criteria while patients await transplantation. In general, for patients within Milan criteria, ablative therapies are used if the expected waiting time until transplantation is greater than 6 months [28].

HCC recurrence following transplantation usually, but not always, manifests within the first 2 years of transplantation and is more likely to occur in patients with more extensive pre-transplant tumor burden [29]. Chemotherapy with agents such as doxorubicin have been evaluated for use pre-operatively, intra-operatively and post-transplantation with limited results. The focus in preventing post-transplant HCC recurrence has shifted to improving down-staging protocols and careful patient selection prior to transplantation [29,30].

7.1.5 Living vs. Deceased Liver Donor

Although liver transplantation is a viable therapeutic option for patients with HCC, there is a shortage of deceased donor livers, and thus, many patients with HCC, die each year waiting for transplantation. Therefore, living donor liver transplantation (LDLT) which does not require a waiting period has emerged as a potential alternative to deceased donor liver transplantation (DDLT). Initial results from a large ongoing multi-center study of LDLT show promising results, especially at high volume centers, with 1-year survival rate of >80% [31]. LDLT has been compared to DDLT in patients with HCC, and although post-transplantation mortality up to 3 years was equal among these groups, patients who underwent LDLT had higher rates of HCC recurrence [32].

There are several explanations for the higher recurrence rates of HCC in patients who undergo LDLT. One possible explanation is that LDLT patients have more advanced disease and which is why they were not eligible for DDLT [32]. Another explanation is that since LDLT patients have very short waiting times to transplant, the biology of the tumor is less known and patients with more aggressive tumors may have been unknowingly selected [32]. Finally, it has been hypothesized that the LDLT surgery itself differs from the DDLT surgery in that it may lead to more tumor manipulation causing tumor embolization [32].

Donor risk is also a concern when considering LDLT. A survey describing 449 living donor transplantations performed in United States reported complications in approximately 14% of donors with one donor death [33]. Complications included bile duct stricture and leak, requirement of blood transfusion, infection, need for rehospitalization, portal vein thrombosis, and pulmonary embolism [32,34]. Worldwide, there have been 9 reported donor deaths and 3 donors have required liver transplantation [34]. The estimated donor mortality risk is 0.2–0.5% [34].

Ethical considerations, donor risk, and recipient outcomes are not yet fully understood in LDLT and should be considered carefully prior to undergoing this modality of therapy for HCC. A recent study analyzed UNOS data regarding outcomes of patients transplanted with HCC. Overall, HCC patients with MELD exceptions had similar survival rates as those who did not have HCC; however, in a subgroup analysis, patients with tumors 3–5 cm had worse survival [25]. This analysis also showed that when adjusting for MELD scores, patients with HCC MELD exceptions had worse post-transplant survival than those with similar MELD scores who did not have HCC [25]. This study has important implications as the transplant community continues to refine the allocation system to create an equitable environment for patients with HCC to compete for transplantable livers.

Conclusion

As described in Chap. 2, in the development of an Information Technology System for Predictive, Preventive and Personalized Medicine (ITS-PM), a wide variety of clinical parameters will be identified and categorized in a Multi-Entity Bayesian Network (MEBN). The MEBN will be used to generate patient-specific Digital Patient Models (DPMs) to facilitate diagnosis, prognosis, and treatment selection, i.e. Model Guided Therapy (MGT). The following have been identified as key issues relating to PPPM and surgical treatment for HCC:

1. Tumor characterization, such as size, number, and vascular invasion;
2. The patient's clinical status, particularly the presence of cirrhosis, the degree of portal hypertension, and liver functional reserve;
3. Pre-operative management, such as patient selection for resection or transplantation, choice of donor, and down-staging and bridging therapies;
4. Surgical techniques, including techniques to minimize blood loss during surgery and to ensure an adequate liver remnant.

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