Chapter 16
Diagnosis and Management of Hepatocellular Carcinoma

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Key Learning Points

- HCC is the sixth commonest cancer worldwide and the third commonest cause of cancer death.
- HCC is associated with cirrhosis in western populations, but can occur in non-cirrhotics especially in eastern populations with chronic hepatitis B infection.
- The role of surveillance remains controversial, although meta-analyses and international liver organizations support its use.
- The BCLC classification is used by most western centres to stage disease and to guide the most appropriate therapy.
- Potentially curative treatments are commonly defined as liver resection, ablation and liver transplantation.
- Stereotactic body radiotherapy (SBRT) is likely to gain greater use in the future across multiple disease stages, e.g. BCLC 0-C.
- Non-curative disease is classically defined as treatment with transarterial chemo/bland embolization, radioemboli-

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T. Cross (ed.), *Liver Disease in Clinical Practice*, In Clinical Practice, https://doi.org/10.1007/978-3-031-10012-3_16

zation for intermediate (BCLC B) and sorafenib, lenvatinib or immunotherapy for advanced (BCLC C disease).
- The introduction of immune-oncology is likely to revolutionize the management of patients with advanced HCC and may find a role in intermediate stage disease.
- Expanding the criteria for liver transplant and the role of downstaging to within transplant criteria is a source of ongoing exploration.

Case Study

A 67-year old man with cirrhotic genetic haemochromatosis (GH) and a history of alcohol excess attends the radiology department for his 6-monthly liver ultrasound scan. The scan shows two lesions which had not previously been seen measuring 20 and 29 mm, respectively. He is otherwise well and has no other co-morbidities. His blood results are as follows: albumin 44 g/dL, AST 36 IU/L, bilirubin 15 μmol/L, creatinine 87 μmol/L, sodium 143 mmol/L, alpha-fetoprotein 4 μmol/L, platelet count 67 × 10^9/L and PT 12 s. He is fit and well and exercises regularly. He has taken no alcohol for 10 years once he was diagnosed with cirrhosis.

An MRI is organized and this confirms the presence of two liver lesions with arterialization in the arterial phase and washout in the portal venous phase.

1. Which of the following statements are true?

   (a) Genetic haemochromatosis is not associated with HCC.
   (b) HCC can develop in the absence of cirrhosis.
   (c) Alpha-fetoprotein is a good screening test for patients at risk of HCC.
   (d) Staging CT Chest, abdomen is mandated to exclude extra-hepatic disease.
   (e) Cardiovascular disease should be excluded.

2. Which of the following treatments would be appropriate (true) in this case?

   (a) Liver resection
   (b) Immuno-oncology
   (c) Transarterial chemoembolization
   (d) Liver transplantation
   (e) Ablation of HCC (microwave, radiofrequency, cryoablation).

Introduction

Hepatocellular carcinoma (HCC) is the sixth commonest form of cancer and is the third commonest form of cancer related death worldwide [1]. The development of HCC is closely related with the presence of cirrhosis. In African and Asian populations HCC may be seen in the absence of cirrhosis. It is a disease with a worldwide distribution, but is more prevalent in regions where both chronic hepatitis B (CHB) and chronic hepatitis C infections (CHC) are endemic [2]. This means that HCC is more common in parts of Africa, South East Asia and the Far East. The existence of viral co-infections (human immunodeficiency virus (HIV) and hepatitis delta infection (HDV)) further heightens the risk of HCC [1, 3]. In Europe and North America there has been a rise in the prevalence of HCC caused by alcohol, non-alcoholic steatohepatitis (NASH) and CHC infection. The introduction of universal vaccination for the prevention of CHB infection was recommended by the World Health Organization in 1990 and would have an impact on the number of future cases of HCC. Studies have indicated that treating both CHB and CHV reduces the risk of the future development of HCC [4].

Diagnosis of Hepatocellular Carcinoma

HCC is either diagnosed as a first clinical presentation where it may be suspected from clinical imaging or it may be found during ultrasound surveillance. Ultrasound scanning is used in surveillance for HCC. Six-monthly scans are recommended in patients with cirrhosis or patients with CHB infection in whom there is a family history of HCC [5]. The role of PET imaging in HCC diagnosis and staging is currently not recommended in the standard clinical work-up for these patients.

Once a lesion has been identified the diagnosis of HCC is made on the presence of characteristic features of a HCC using dynamic imaging in a patient deemed to be at risk of the disease. Dual phase CT and contrast MRI using gadolinium or primovist contrast agents are used, although diffusion weighted imaging is increasingly utilized [6, 7]. The classical HCC nodule demonstrates arterialization during the arterial phase of the scan with subsequent washout observed in the lesion during the porto-venous phase of the scan (Fig. 16.1). In cases where the lesions are small (≤1 cm) an interval scan using the same modality in 3–4 months is often recommended to determine if there is any change in size or if the lesion takes on features more suggestive of a HCC. In cases where the nature of the abnormality is still unclear a lesional biopsy is recommended to secure a histological diagnosis [8].

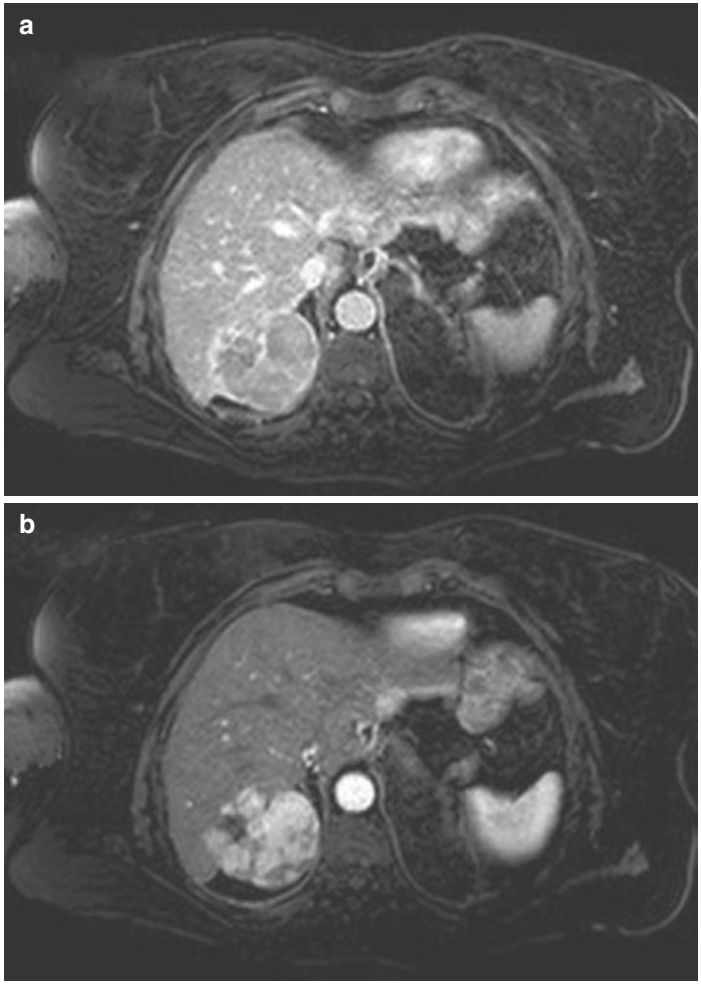

FIGURE 16.1 MRI liver with gadolinium enhancement. (**a**) A large hypovascular lesion is seen in segment 7 on the delayed phase imaging. This shows arterialization in the arterial phase (**b**) and then shows washout in the portal venous phase and venous phase (**c**). This lesion demonstrates the classical hallmarks of a HCC

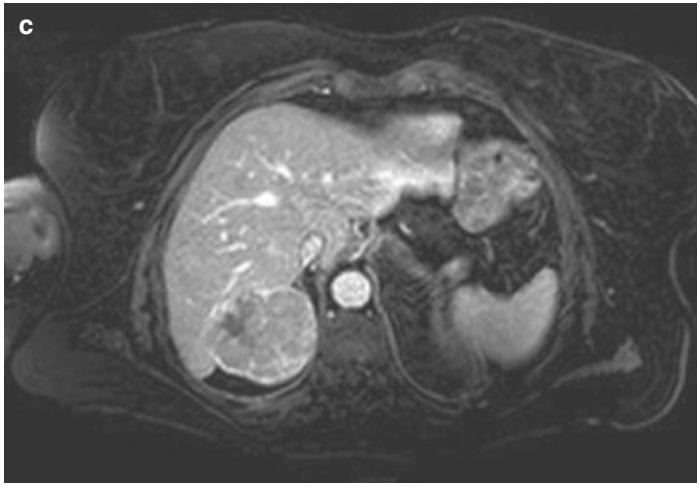

Figure 16.1 (continued)

Current Treatment Modalities for Treatment of Hepatocellular Carcinoma

Treatment for HCC broadly falls into three categories: curative, non-curative and palliative. A framework is required to help clinicians decide on the optimal treatment for their patients. It is possible to divide this approach into tumour characteristics (i.e. tumour size, number of nodules, AFP, the presence of metastases and portal vein invasion) and the patient characteristics (e.g. Child-Pugh score, co-morbidities, age, frailty, ascites, jaundice). Most clinicians use the Barcelona Clinic Liver Cancer (BCLC) staging system [9] (Fig. 16.2). Briefly, disease is categorized into five groups: Stage 0 a single small lesion ≤2 cm in a non-cirrhotic liver (optimal treatment—liver resection); Stage A—a solitary lesion ≥2 cm but ≤4.5 cm or three lesions the largest of which is 3 cm, in the absence of extra-hepatic disease or where there are features of portal hypertension (optimal treatment liver transplantation); Stage B—a solitary lesion >5.5 cm or >3 liver lesions, the largest of which is >3 cm (optimal treatment loco-regional

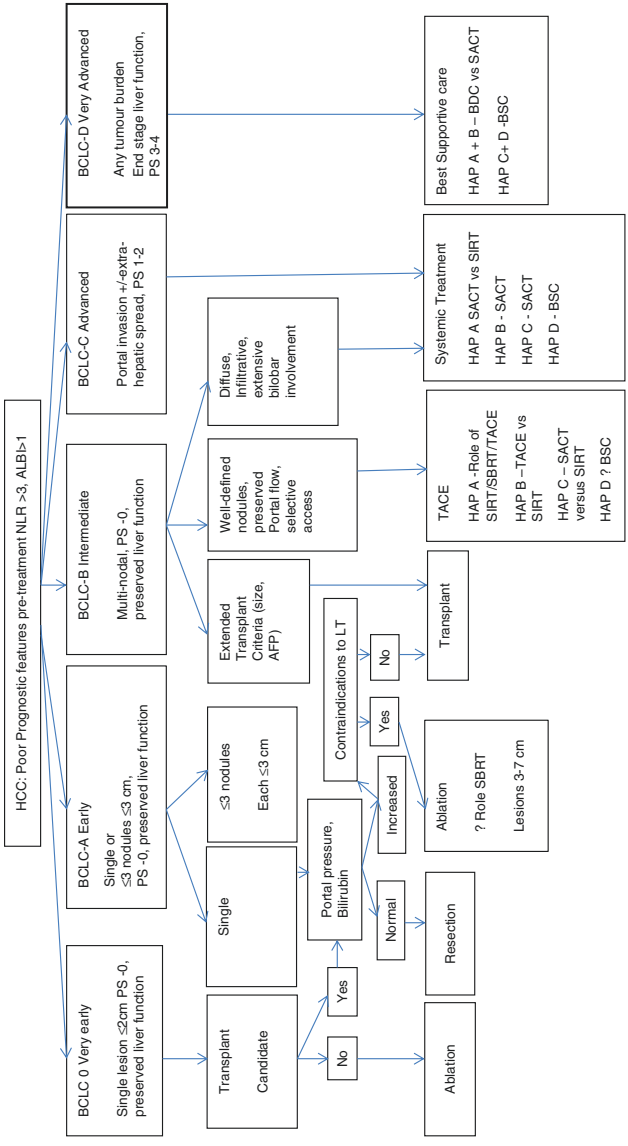

FIGURE 16.2 The proposed modification of the current BCLC staging system. The modified liverpool BCLC algorithm for the management of patients with hepatocellular carcinoma [4]

therapies, e.g. transarterial chemo/radioembolization (TACE/TARE) and ablative techniques (for lesions ≤3 cm)); Stage C—liver nodules of any size but in the presence of tumour thrombus in the portal venous system or extra-hepatic disease, e.g. lymph nodes, lung, bone metastases (optimal treatment immune-oncology, Sorafenib, lenvatinib, etc.). Stage D—HCC in the presence of decompensated liver disease, e.g. ascites, liver dysfunction (optimal treatment—best supportive care).

These stages only act as a guide and there is some fluidity between them. Other staging methods include the CLIP [10], the Milan criteria [11] and recent the Hong Kong Liver cancer staging system [12]. The Milan criteria identified a group of patients who would benefit from liver transplantation (LT). Mazzaferro and colleagues systematically reviewed outcomes from LT in a cohort of Italian HCC patients and discovered that the outcomes from LT were good in patients with single lesions ≤4.5 cm or when there are three lesions the largest of which is no bigger than 3 cm. This landmark study has formed the basis of LT practice for nearly 20 years. Other groups have tried to see if those boundaries for liver size can be pushed a little further by assessing outcomes in larger tumours or where more than three HCC nodules are present, e.g. UCSF criteria [13, 14], metroticket [15]. In reality, the majority of patients are not candidates for LT and LT is certainly not going to address the underlying causes of HCC and the diseases that lead to its development. Thus, attention has been re-focused on methods to better select patients who will derive benefit from loco-regional therapies and to predict who is at greater risk of disease recurrence after LT, or who could be managed to provide good life expectancy in the absence of LT. These additional methods include The ART strategy [16], the HAP score [17] and the Duvoux score [18] (Table 16.1).

Table 16.1 Prognostic models used to guide the management of hepatocellular carcinoma

Author	Score	Parameters
Bruix et al. [6]	Barcelona Clinic Liver Cancer stage	See Fig. 16.2
	Hong Kong Liver Cancer	
A more complicated version of BCLC derived from a large cohort from Hong Kong aiming to identify patients who may benefit from more radical treatments that considered under BCLC. Needs validation outside of Asia		
Mazzaferro et al. [11]	The Milan Criteria	×1 HCC ≤5 cm
		Or ×3 lesions ≤3 cm
If within criteria good results from LT, i.e. 5 year survival ~70%		
Yao et al. [13]	The UCSF criteria	×1 lesion ≤6.5 cm
		×3 lesions largest <4.5 cm
		Total tumour diameter <8.5 cm
Able to achieve LT results comparable with Milan criteria with expanded access		
Mazzaferro et al. [15]	The Metroticket score	Diameter of largest nodule
		Sum of hepatic malignant nodules
		"Up to seven criteria"
If sum of diameter of largest lesion and number nodules <7–5 year survival ~70% for LT		

Table 16.1 (continued)

Author	Score	Parameters
Duvoux et al. [18]	The Duvoux score	Tumour diameter ≤3 cm = 0, 3–6 cm = 1 points >6 cm = 4 points Number of nodules 1–3 = 0 points ≥4 = 2 points AFP ≤100 = 0 points, 100–1000 = 2 points >1000 = 3 points
Score > 2 associated with greater risk of disease recurrence post LT		
Kadalayil et al. [17]	The HAP score	AFP >400 ng/mL = 1 Tumour >7 cm = 1 Albumin <36 g/dL = 1 Bilirubin >17 μmol/L = 1
Sum of scores HAP A = 0, HAP B = 1, HAP C = 2, HAP D > 2 allows identification of patients of risk of decompensation after TACE. Median survivals HAP A 27.6 months, HAP B 18.5 months, HAP C 9 months, HAP D 3.8 months		

Table 16.1 (continued)

Author	Score	Parameters
Hucke et al. [16]	The ART strategy	Radiologic tumour response Present = 0, absent = 1 point AST rise >25% Present = 4 points, absent = 0 Child-Pugh score increase 1 point rise = 1.5 points ≥2 points = 3 points Absent = 0 points
Used to identify patients who will not benefit from TACE. A score of >2.5 identifies patients who do not benefit from further TACE		

The Role of HCC Surveillance in at Risk Patients

The rationale for screening and surveillance is simple. If one looks for a particular disease in a population at risk for that condition at regular intervals, it is more likely that, should that disease arise, it will be detected at an earlier stage at which point curative treatment would be possible. It is known that patients who develop HCC tend to have liver cirrhosis and are older [19]. The recommendations from EASL, AASLD, are that a liver ultrasound examination should be performed on a 6-monthly basis for all patients with cirrhosis or patients with CHB where there is a family history of HCC. AFP is no longer recommended as a screening tool [1].

For surveillance programmes to be effective the test used must be accurate, cost-effective, readily available and targeted to the right population. Liver ultrasound is readily available in many health care systems, but does have problems. The technique is user dependent, and for a programme to work best it would be preferred to have dedicated practitioners who just do USS HCC surveillance. Ultrasound is less good in patients who are obese and those with narrow rib spaces. It is also challenging in patients with dysplastic or regenerative nodules, at which point further imaging is mandated and then subsequent follow-up imaging becomes more problematic (and expensive). In a UK study it was discovered that the provision, organization and uptake of ultrasound surveillance for HCC were poor [19].

A meta-analysis of 32 studies comprising 13,367 patients concluded that ultrasound has a low sensitivity of 47% (95% CI 33–61%) to detect early-stage HCC in patients with cirrhosis [20]. Therefore, more work needs to be done in order to define the best surveillance strategies for different patient cohorts.

Are there ways in which the accuracy of surveillance could be improved? A statistical model called the GALAD score has been proposed as a tool for determining the risk of HCC in individuals with chronic liver disease. The score comprises gender, age and serological tumour markers including AFP-L3, α fetoprotein (AFP) and des-carboxy-prothrombin. The score has been validated in a large multicentre, multicontinent study comprising 6834 patients. The AUC for GALAD in all cohorts examined was greater than 0.90 [21].

The use of cross-sectional imaging modalities such as CT or MRI is not recommended for surveillance due a lack of data on efficacy and concerns regarding cost-effectiveness and potential harm related to radiation and contrast exposure. Although the role of non-contrast MRI is an imaging modality under investigation as a possible alternative to patients who are not optimal candidates for USS.

Other potential biomarkers related to HCC have been identified and have the potential to be utilized as HCC sur-

veillance markers. However, few have yet been evaluated in phase 2 studies [22].

Further work is required until a more tailored approach to HCC surveillance is possible. The emergence of reliable novel disease biomarkers would also be a significant step forward.

The Role of Liver Transplantation in the Management of HCC

The definitive treatment for the majority of HCC cases is LT. This is because transplantation removes both the cancer and the cirrhotic liver that is susceptible to further tumours and decompensation. The role of LT in the management of HCC is well-defined, but some areas require further investigation.

The Role of Downstaging

Is it possible to downstage a tumour such that it would then fall within transplantable range? This is a question that has puzzled transplant clinicians since the advent of LT as a meaningful treatment modality. If a lesion(s) is outside criteria but can be brought within criteria by a treatment, e.g. transarterial chemoembolization, are the outcomes similar to those patients who do not require "downstaging"? A meeting of international experts on the role of LT for the management for HCC proposed three statements on this matter: (1) the criteria for successful downstaging should include tumour size and the number of viable tumours; (2) AFP concentrations before and after downstaging might add further information and (3) based on existing evidence, no recommendations can be made for preferring a specific loco-regional therapy for downstaging over others [23].

There is a growing body of evidence that liver transplant for HCC beyond Milan criteria is not associated with worse outcomes. Several different models exist with expanded crite-

ria for cadaveric liver transplantation for HCC. The University of California San Francisco (UCSF) criteria describes a solitary tumour ≤6.5 cm or ≤3 tumours with the largest ≤4.5 cm. The "up to seven" criteria include a combination of tumour maximum size and number of lesions in patients without microvascular invasion. The Clinic of Universidad of Navarra (CUN) criteria describes 1 tumour ≤6 cm or ≤3 tumours with the largest ≤5 cm. The criteria described by Toso et al. includes total tumour volume and AFP. The criteria of the University of Hangzhou involve total tumour diameter, histological grade and AFP. Onaca et al. describe criteria of a solitary tumour ≤6 cm or 2–4 tumours ≤5 cm.

All of these criteria have been shown to have favourable outcomes that are comparable to patients transplanted within Milan criteria [24].

Treatment on the Waiting List

The anxiety with any malignant process is that, if left alone, the cancer will continue to grow and progress. If the tumour grows beyond a certain size or number of tumour nodules curative therapy will no longer be possible. An additional problem is that, under the current system of organ donation and allocation, the wait time for a LT is unpredictable and is influenced by factors such as recipient and donor blood group, weight and height. Interestingly, some authors have said that wait time does not influence outcomes [25]. Patients who do well after a long wait list time may be those with the less aggressive tumour biology. In order to maintain patients within criteria some liver transplant centres will offer locoregional therapy by way of ablative techniques (microwave, radiofrequency ablation) or embolic approaches (transarterial embolization, transarterial radio-embolization). The aim is to maintain patients within transplant criteria whilst awaiting the operation. An ablation technique will have no impact on availability of for LT but for patients who undergo chemoembolization patients are suspended from the wait list for 4 weeks after treatment because of the impact on white cells

and the perceived increased risk of infections at the time of LT. There is also a concern that TACE may cause hepatic decompensation and make patients too unfit for surgery. It is for this reason that some centres are reluctant to give TACE to patients on the waitlist. But, in the face of unpredictable wait times for cadaveric organs or deceased non-heart beating donors, other centres have felt compelled to offer loco-regional treatment to optimize their patients' chances of progressing onto the liver transplant. International experts concede that treatment may be appropriate where wait times are likely to be in excess of 6 months [23, 26].

Liver Transplantation as Salvage Therapy

Given the continuing rise in the number of patients being considered for LT with only a modest increase in the donor pool, there has been a call to optimize the use of available organs. The reason behind this is due to the increasing number of HCC patients who occupy places on the liver transplant waitlist. This is felt to be disproportionate in comparison to the actual disease burden presented by HCC. Some clinicians feel that increasing the number of transplants performed for HCC may have a deleterious impact on other patients awaiting LT, particularly in medical systems where HCC patients are given some prioritization. In a model where LT and liver resection were at one time regarded as the only effective (curative) treatment, the advent of new techniques such as ablative therapies potentially offer good treatment for small HCCs. The 1-year mortality from liver transplant of 9% at 1 year, for frail patients, the risks of major surgery may outweigh the risks. Thus, patient selection is a vital. For small HCCs (i.e. $\leq$2 cm), in the absence of cirrhosis or significant portal hypertension (<10 mmHg), these patients can be offered liver resection, an ablation technique and if unfit for anaesthetic could be considered for stereotactic body radiotherapy (SBRT). Unfortunately, despite small lesions being present surgery is not often possible, but ablation is possible for the majority of these patients. Ablation approaches have only provided an effective treat-

ment zone of up to 3 cm. If there is well-preserved liver function, there is no barrier for more than one lesion being treated. Newer ablative techniques may allow a treatment zone for lesions up to 5 cm in maximum diameter.

Alpha-fetoprotein is a tumour marker that is elevated in some cases of HCC. It is no longer used as a screening tool but a useful prognostic tool. Very high levels of AFP portend a poor outcome and studies have suggested that levels >400 IU/L at the time of liver transplant are associated with a higher risk of disease recurrence post-transplant [27, 28]. So in terms of creating a model that helps identify patients who may or may not benefit from LT it can be seen that a system consisting of tumour size, number of tumour nodules and AFP level might have some utility. Duvoux and colleagues devised a scoring system consisting of these three variables and assigned different scores according to tumour size, number of nodules and AFP [18]. It is possible that using this approach, patients could be stratified to loco-regional treatment before liver transplantation, and that this could be used to help reduce the number of LTs performed for HCC where survival might be comparable with loco-regional techniques.

Delisting HCC Patients

One of the most difficult decisions transplant clinicians need to make is to decide when LT is no longer in the interest of the patient. The patient is delisted if the HCC acquires unfavourable characteristics that are incompatible with long term survival (i.e. <50% chance of 5 year survival). This includes all the poor prognostic indicators that are assessed prior to listing, i.e. increase in tumour size beyond accepted listing criteria, tumour invasion of the portal vasculature and extra-hepatic disease (lymph nodes, lung and bone metastases). Other factors include factors that are not directly due to the tumour, e.g. cardio-respiratory illness, frailty, the development of additional malignancies and factors that would make anaesthesia and surgery too high risk, e.g. morbid obesity.

Improving Existing Therapies

The majority of patients with HCC are not candidates for LT and it is natural that the pressure for new therapies has been for this group of patients (BCLC B and C). The advent of transarterial embolization techniques was a step forward and for some time there was a debate over whether there was any survival benefit conferred by administering a chemoembolization over a bland embolization technique (i.e. embolization of feeding vessel to the tumour). The demonstration by Llovet and Bruix suggesting the benefits of TACE has led investigators to seek ways of improving the efficacy of this treatment [29]. Initially, the chemotherapeutic agents (doxorubicin, cisplatin) were mixed with lipiodol and administered as a mixture. More recently drug-eluting beads have been manufactured. Interestingly there is no study to demonstrate which chemotherapeutic agent is the best in HCC. The optimal timing and selection of patients is important. Techniques such as the ART strategy and the HAP score have been introduced to help identify those patients who will derive less benefit from treatment. Researchers have also been exploring ways in which to increase the impact of treatment. Pre-treatment with systemic doxorubicin has been suggested as one way to enhance the lethality of chemoembolization and a recent paper suggested that metformin may have a role in reducing the risk of developing HCC in patients with NASH and alcohol-related cirrhosis and may aid in improving the efficacy of future treatment [30]. There has also been more interest in the use of transarterial radio-embolization (TARE). Recent studies with TARE have been promising and it has the benefit of being applicable in patients with portal vein thrombosis, in whom conventional TACE would be contra-indicated. The effect of the treatment is delivered locally and appears to have a sustained effect. This means that a single, rather than multiple, treatment, is possible. Yet, TARE is time-consuming and requires interventional radiology support. Treatment requires two radiology sessions, the first, to plan

treatment and to look for parasitic supplies that might take some of the radioactivity away from the tumour zone and towards healthy tissue in the lungs, stomach and small intestine. This can lead to a debilitating radiation pneumonitis or gastritis that can lead to significant morbidity and even death. As such, assessing for parasitic supplies and shunting (with the aid of nuclear medicine) is an essential part of the work-up. A parasitic supply is defined as tumour vascularizations and new vessels derived from neighbouring organs or structures, and supplemental to the normal blood supply of the diseased organ. Only once shunts have been excluded, or are below a certain level, can treatment be given.

Selective internal radiation therapy (SIRT) is now approved by NICE for the treatment of unresectable HCC in patients with compensated liver disease for whom TACE is not appropriate. Both the SARAH trial and the SIRveNIB trial were phase 3, multicentre, open label investigator lead trials comparing SIRT with sorafenib in patients with BCLC C disease. Patients with recurrent disease after surgery or thermoablative therapy and patients who have failed TACE were also included in the SARAH trial. Both trials showed no survival difference between sorafenib and SIRT. However, there were fewer adverse events in patients treated with SIRT which may make this the preferable choice [31, 32]. More work needs to be done in order to define the relevant population that will have maximum benefit from SIRT over other systemic treatment options.

Stereotactic body radiation therapy (SBRT) is a non-invasive technique for delivering high doses of radiotherapy to a lesion whilst minimizing damage to surrounding structures and organs. This technique might be preferred for lesions in close proximity to structures such as blood vessels, bile ducts, the diaphragm, etc. There is emerging evidence for the use of SBRT in patients with early-stage HCC who are not fit for surgical resection or ablative therapies as well as in patients with advanced disease who have failed other treatments, e.g. TACE [33]. SBRT is thus a further tool in the clinicians armamentarium. However, more work needs to be done

to better define the patient cohorts that will confer the most benefit from this treatment option.

Systemic Therapy

Up until recently the only treatment option for patients with advanced metastatic HCC (BCLC C), in the absence of liver decompensation, was sorafenib. The SHARP trial demonstrated a median survival with sorafenib of 10.7 months versus 7.9 months with placebo (hazard ratio 0.69, 95% CI 0.55 0.88 $P = 0.00058$) [34].

There are now other treatment options for this group of patients. An open label, phase 3, multicentre trial comparing lenvatinib with sorafenib in first line treatment of unresectable HCC demonstrated non-inferiority of lenvatinib [35].

Both treatments are now recommended by NICE as options for patients with Child-Pugh A cirrhosis and an ECOG performance status of 0 or 1, who have not received prior systemic therapy for HCC.

Patients who have previously been treated with sorafenib can be offered cabozantinib, a vascular endothelial growth factor (VEGF) inhibitor. A double-blind, placebo controlled, randomized phase 3 trial demonstrated an improved overall and progression free survival for patients receiving cabozantinib compared to placebo. Median overall survival was 10.2 months with cabozantinib and 8.0 months with placebo (hazard ratio for death 0.76, 95% CI 0.63–0.92, $P = 0.005$) [36].

The era of immunotherapy has now extended to hepatocellular carcinoma and is yet another option for first line systemic therapy in patients with advanced disease. A global, open label, phase 3 trial compared Atezolizumab plus Bevacizumab (n = 336) with sorafenib (n = 165) in patients with unresectable HCC, who had not previously received systemic therapy. The immunotherapy regime resulted in improved overall and progression free survival compared with sorafenib. Overall survival at 12 months was 67.2% (95% CI 61.3–73.1) with atezolizumab-bevacizumab and 54.6% (95% CI 45.2–64.0) with sorafenib [37].

Early results from a phase 1b study have shown promise for the addition of lenvatinib to the immunotherapy agent Pembrolizumab for patients with unresectable HCC [38] and this was later followed up in the Keynote 240 study [39]. In the study 413 patients were randomly assigned. These patients had been previously treated with sorafenib. As of January 2, 2019, median follow-up was 13.8 months for Pembrolizumab and 10.6 months for placebo. Median OS was 13.9 months (95% CI, 11.6–16.0 months) for pembrolizumab versus 10.6 months (95% CI, 8.3–13.5 months) for placebo (hazard ratio [HR], 0.781; 95% CI, 0.611–0.998; $P = 0.0238$). In this study, OS and PFS did not reach statistical significance per specified criteria. The results are consistent with those of KEYNOTE-224, supporting a favourable risk-to-benefit ratio for pembrolizumab in this population.

The important consideration with any treatment is the prospect of adverse effects of treatment. The clinical trials of immuno-oncology (IO) have highlighted some issues.

1. Bleeding: In the IMBrave 250 study there was an increased risk of variceal bleeding in the IO arm versus Sorafenib (25% versus 15%), even though both groups had 26% variceal rate in both arms. Most clinicians would advise a recent oesophago-gastro-duodenoscopy (OGD) prior to treatment. Some clinicians will not give IO if the patient has had a variceal bleed in the preceding 6 months, although others suggest that treatment could start from 14 days post bleed. Some groups have tried to determine guidance. The London HOB oncology group came up with the following guidance before commencing Atezo/Bev: (a). Variceal bleed last 6 months not for Atexo/Bev, (b). OGD within 6–12 months and no varices or on B-Blockade—start Atezo/Bev, (c). No varices start Atezo/Bev. It is likely that this guidance will evolve. In addition to bleeding some patients may also develop thrombosis, e.g. portal vein thrombosis (PVT). The bleeding and clot formation have been blamed mainly on the Bevacizumab and so some clinicians would consider a switch from dual to monotherapy

with Atezolizumab alone, but this decision should best be made within a MDT/cancer board meeting.

2. Hypertension and Proteinuria: Patients at increased risk of kidney disease, e.g. diabetes, and patients with chronic viral hepatitis should be screened for proteinuria and have baseline renal function assessed. If renal dysfunction or proteinuria is found a referral to the renal team is mandated. Where hypertension does exist treatment with angiotensin converting enzyme inhibitors or angiotensin II blockers is often effective.
3. Diarrhoea: Mainly of the IO treatments can instigate immune mediated colitis and occasionally hepatitis. Infective causes of diarrhoea should be excluded as should inflammatory bowel disease or malignancy. One should consider the most common causes. If a diarrhoea screen is negative, a flexible sigmoidoscopy or colonoscopy is needed and biopsies taken to elicit the cause. An immune mediated colitis (and hepatitis) often resolves with high dose corticosteroids and occasional may need the addition of other immunosuppressive agents, e.g. mycophenolate mofetil, tacrolimus. The IO drug may need to be reduced or even stopped in some circumstances, but can sometimes be re-introduced.

Getting More from Sorafenib

Clinicians have wondered if adding sorafenib to patients undergoing loco-regional therapies such as ablation or chemoembolization might confer a survival advantage. However, the evidence so far does not support this theory.

The STORM trial was a phase 3, randomized, double-blind, placebo controlled trial assessing the use of sorafenib as adjuvant treatment following surgical resection or ablation. The data failed to show any benefit from sorafenib compared with placebo in recurrence free survival following these treatments [40].

TACE II was a multicentre, randomized, placebo controlled, double-blind phase 3 trial looking at adjuvant sorafenib following TACE in patients with unresectable HCC confined to the liver. The results showed no benefit from sorafenib in progression free survival [41].

Researchers have wondered if drug combinations might exacerbate the efficacy of sorafenib. But using sorafenib with erlotinib, everolimus and BIIB IGFR mAb, has produced disappointing results, with problems due to toxicity or because no benefit was proven with combination.

Stereotactic body radiation therapy (SBRT) is a non-invasive technique for delivering high doses of radiotherapy to a lesion whilst minimizing damage to surrounding structures and organs. This technique might be preferred for lesions in close proximity to structures such as blood vessels, bile ducts, the diaphragm, etc. There is emerging evidence for the use of SBRT in patients with early-stage HCC who are not fit for surgical resection or ablative therapies as well as in patients with advanced disease who have failed other treatments [42]. However, more work needs to be done to better define the patient cohorts that will confer the most benefit from this treatment option.

Conclusion

In the future clearer targets will need to be derived from our understanding of the biology of these tumours. This will help inform the best treatment for each patient based upon knowledge of the patient and their tumour. There remain lots of unanswered questions. Improved methods of surveillance and diseases stratification are needed, and given the problems with ultrasound as a surveillance tool it might be useful to have biomarkers built in to trial design to allow identification of new surveillance tools (and markers of tumour biology). Immunotherapy is an exciting prospect that is in its infancy but is currently an additional option for patients with advanced disease. The best therapy may be required in com-

bination and with greater understanding of genetics and risk profiling it may be possible in the future to tailor the best treatment for each patient. In addition, with new therapies more questions shall arise such as how should these new treatments be used in the context of liver resection, liver transplantation (pre-and post-surgery), and what role in loco-regional therapies. There is much to do, but this is an exciting time to be involved in the treatment of patients with HCC.

Answers to Questions

1. Which of the following statements are true?

   (a) Genetic haemochromatosis is not associated with HCC. **False—there is a strong association with HCC**
   (b) HCC can develop in the absence of cirrhosis. **True**
   (c) Alpha-fetoprotein is a good screening test for all patients at risk of HCC. **False—only 30% of cases of HCC secrete alpha-fetoprotein. It is a poor screening tool but can be used as a prognostic indicator and marker of aggressive tumour biology**.
   (d) Staging CT chest, abdomen is mandated to exclude extra-hepatic disease. **True—the presence of extra-hepatic disease would preclude liver resection and transplantation and is therefore an important test to do**.
   (e) Cardiovascular disease should be excluded. **True—GH is associated with cardiovascular disease (possible because of the association with diabetes mellitus) and must be actively sought in a transplant assessment process**.

2. Which of the following treatments would be appropriate (true) in this case?

   (a) Liver resection. False—The low platelet count suggests portal hypertension and thus resection may be best avoided. Given the high risk of diseases recurrence in the remnant liver and the multifocal nature of diseases (particularly if disease in different lobes), liver transplantation would be a better choice.

(b) Immuno-oncology. **False—This treatment is reserved for patients with extra-hepatic disease in the absence of hepatic decompensation (BCLC C)**.

(c) Transarterial chemoembolization. **False—This is reserved for patients with hepatic disease who are outside resection or liver transplant criteria (BCLC B). Although this modality may be used if thermal ablations are considered too hazardous (e.g. challenging anatomical location) or if the patient is not fit for an ablation, e.g. not fit for general anaesthetic**.

(d) Liver transplantation. **True—This is the optimal treatment**.

(e) Ablation of HCC (microwave, radiofrequency, cryoablation). **True—given that the wait time for transplant may be beyond 6 months ablation is recommended as a bridge to transplant in these cases**.

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