Annals of Medicine and Surgery 3 (2014) 71–76

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.annalsjournal.com

Review

How grim is hepatocellular carcinoma?

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ARTICLE INFO

Article history:
Received 4 March 2014
Received in revised form
7 May 2014
Accepted 25 June 2014

Keywords:
Resection
Ablation
Transplantation
Sorafenib
Prevention

ABSTRACT

Hepatocellular carcinoma (HCC) is a complex disease and a major cause of death in high endemic areas of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. HCC has gone from being a universal death sentence to a cancer that can be prevented, detected at an early stage and effectively treated. Liver resection or tumour ablation techniques may be effective bridge to liver transplantation if they fulfill the Milan criteria. The areas of progress in HCC are in the control of HBV or HCV and the development of adjuvant or neoadjuvant therapies.

1. Introduction

Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers and is a major global health problem within excess of 1million cases per year. More than 80% of cases are found in Africa or East Asia (100 cases per 100,000 population in S. Africa and S.E. Asia) [1,2]. The rising incidence in the West is due to Hepatitis C (HCV) epidemic and the increase in prevalence of chronic alcoholic liver disease [3]. It usually affects patients in their early fifties but earlier onset (25–40 years) in Africa. This is probably related to their earlier exposure to HBV or HCV viruses with men having a three- to eight-fold greater risk of developing HCC than women [4]. Treatments share a high incidence of tumour recurrence due to the persistence of the underlying cirrhosis that represents a preneoplastic condition [5,6]. The early enthusiasm for transplantation for large, non-resectable primary malignancy was dampened by the high recurrence rate. It is the small HCC in the setting of cirrhosis which is better treated by transplantation than resection [7]. The enormous progress of liver transplantation with the widening spectrum of disease processes amenable to it have added to the organ shortage and need for alternatives [8]. The problem of using chemotherapy in HCC stems from the coexistence of two diseases (HCC and liver cirrhosis) and the chemoresistant nature of HCC [9].

2. Aetiology/pathogenesis of HCC

A total of 70–90% of HCC develop on a background of cirrhosis particularly in relation to the post hepatitis liver (HBV and HCV infection), alcohol and haemochromatosis (Fig. 1). In cirrhosis, HCC occurs due to chronic injury, regeneration and dysplasia [5]. A total of 7–20% of primary liver malignancies occur in non-cirrhotic liver and the prevalence of HBV infection is less than 10% in these cases. This fibrolamellar variant (FLC) is most frequently observed in the Western hemisphere, and at younger age (between 20 and 30 years) than HCC [10]. Ingestion of aflatoxin by *Aspergillus flavus* contamination of imperfectly stored crops causes the mutation of the P53 suppressor gene and is an independent risk factor. [11] The HBV is directly oncogenic by incorporating into host genetic material even in the absence of cirrhosis. It takes 10 years to develop chronic hepatitis, 20 years to develop cirrhosis and 30 years to develop HCC which explains why it usually affects patients in the 50–70-year age group [12]. Macroscopically, HCC can be solitary or multifocal, nodular or diffuse. It has a great tendency to spread locally and to invade blood vessel particularly the portal vein (32–70%) [5,12]. It may directly invade the diaphragm and colon, rupture and bleed into peritoneal cavity or spread via blood stream leading to distal metastases, in bone, lung, brain, adrenal glands [12]. Tumour differentiation and vascular invasion are important

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http://dx.doi.org/10.1016/j.amsu.2014.06.006

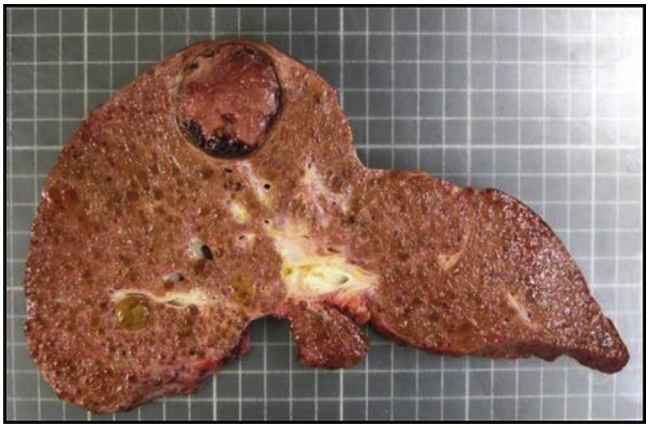

Fig. 1. HCC and micronodular cirrhosis.

predictors of survival after surgical resection or liver transplantation [4,5,8,9].

2.1. Clinical presentation

It is usually asymptomatic, detected by a routine ultrasound during screening in patients with cirrhosis [4]. It should be suspected in patients with cirrhosis when there is deterioration of liver function, acute complications or decompensation of chronic liver disease (ascites, encephalopathy, variceal bleed, jaundice) usually from portal vein thrombosis and the development of upper abdominal pain and fever. Locally advanced disease may present with weight loss, anorexia, abdominal pain and hepatomegaly [10,12]. Spontaneous rupture of HCC occurs in 10–15% of patients with large superficial or protruding tumours and, accounts for up to 10% of deaths from peritonitis and shock [10]. Most HCC patients without treatment die within 6 months of diagnosis [1–5]. The fibrolamellar variant in non-cirrhotic liver of young adults are less aggressive and prolonged survival has been reported even in patients with advanced tumour stage and metastatic spread [10].

2.2. Investigations

The investigations would depend on the mode of presentation and the aims are illustrated (Table 1).

Biopsy is usually not indicated as is considered to carry a risk of tumour seeding along the needle track (1–2%) converting an operable tumour to a non-operable one [4,15]. The model for end-stage liver disease (MELD) score originally developed to assess the prognosis of cirrhotic patients undergoing trans internal jugular peritoneal shunting (TIPS) for intractable ascites is now used to stratify patients on waiting list for transplantation. As the disease progresses whilst on the waiting list a UK model for end-stage liver disease (UKELD) scoring has improved mortality prediction and increased efficiency of allocation of donated livers. The minimum listing criteria is a UKELD score greater than 49 that predicts a greater than 9% 1-year mortality [19].

Serum alpha fetoprotein (AFP) is elevated in only 50–60% of cases, with cirrhotic liver but is useful as a baseline prior to treatment [20]. It is not very reliable as some HCC may have low or no AFP and an adenoma may have high AFP. It may be raised in patients with testicular or germ cell tumours, intrahepatic cholangiocarcimona, gastric and colon carcinomas [10]. Thus the diagnosis must rest on radiological appearance and on histology. [21] However, the presence of a discrete mass within a cirrhotic liver, together with an alpha fetoprotein greater than 500 ng/ml is diagnostic [4,22].

2.3. Staging systems

Several systems have been used, including theTNM, Cancer of the Liver Italian Program (CLIP), Barcelona Clinic Liver cancer (BCLC), Okuda and Japan Integrated Staging (JIS). Several factors have been incorporated into each system, and relate to tumour load and biology (size, number, presence of extrahepatic disease, and presence of vascular invasion), liver reserve (Child-Pugh score or its components, Table 2), and performance status [23,24]. A modified TNM classification still has several limitations. Pathological information is required to assess microvascular invasion which is only available in the 20% of patients treated by surgery. It does not capture information regarding liver function studies or health status [25]. The BCLC staging system (Table 3) is recommended as it has been externally validated in different clinical settings. It is an evolving system that links tumour stage with treatment strategy in a dynamic manner that enables the incorporation of novel advancements in the understanding of the prognosis or management of HCC [26]. Although these systems predict survival, they do not specifically allow selection of patients for potentially curative treatment (resection or liver transplantation). In 1996, the *Milan criteria* were the first to be published that defined a subgroup of patients who were suitable for liver transplantation with a 5-year survival exceeding 70%. [7] The *Milan criteria* are: (a) single HCC <5 cm, (b) three tumours < 3 cm, in the absence of extrahepatic disease and vascular invasion. The expanded University of California, San Francisco (UCSF) criteria: a single HCC <6.5 cm; three

Table 1
Aims of investigations.

• Confirm diagnosis of HCC radiologically	Ultrasound (US) scan detects 2 cm lesions
• Determine extent of liver involvement	Computed tomography (CT) scan with contrast-tumour darker than other cells as HCC does not take contrast Triphasic CT or MRI-hypervascular lesion with peripheral enhancement [4,13,14]
• Exclude extrahepatic disease	CT of chest ± bone scan
• Assess underlying liver disease	CT scan ± biopsy of non-tumour liver if in doubt
• Determine severity of liver disease	Child-Pugh or model for end-stage liver disease (MELD) score [16–18]

Table 2
Calculating Child-Pugh score and classification.

Variable	Score		
	1	2	3
Bilirubin μmol/l	<34	34–51	>51
Ascites	Absent	Slight	Moderate
INR	<1.3	1.3–1.5	>1.5
Albumin, g/l	>35	28–35	<28
Encephalopathy	Grade 0	Grade 1–2	Grade 3–4

Child-Pugh classification	Score	1-Year survival (%)
A – well compensated	5–6	100
B – significant functional compromise	7–9	80
C – decompensated	10–15	45

INR, international normalized ratio.

Table 3
Treatment modalities and outcomes.

The BCLC staging system and treatment allocation			
	Child-Pugh	Treatment	5-Year survival
Stage 0	Child-Pugh A PS 0 Curative treatment (30–40%)	Resection (30–40%)	Overall survival (>60 months) 40–70%
Early stage A	Child-Pugh A Single or 3 nodules < 3 cm PS 0 Curative treatment	Transplantation (if no assoc disease) RF/PEI (if assoc diseases)	Overall survival (>60 months) 40–70%
Intermediate stage B	Child-Pugh B Multinodular Asymptomatic, no vascular invasion or extrahepatic spread PS 0 palliative treament	TACE target 20%	Overall survival (20 months)
Advanced Stage C	Child-Pugh B Portal invasion, N1, M1; PS1–2 Palliative treatment	Sorafenib target 40%	Overall survival (11 months)
Stage D	Child-Pugh C Symptomatic treatment PS > 2	Best supporting care target 10%	Overall survival (<3 months)

PS, performance score.

tumours <4.5 cm, in the absence of extrahepatic disease and vascular invasion were not associated with a reduced disease-free survival after liver transplantation [27].

2.3.1. Localized disease

(a) Liver resection: resection is the only treatment that can offer cure although it is feasible in less than 20% of patients because of local spread and severity of pre-existing cirrhosis. The indications are absence of extrahepatic disease in a patient with no underlying liver disease or Child A cirrhosis [4,28,29]. Minor resections may be considered in patients with early Child B without portal hypertension (i.e. hepatic vein pressure <10 mmHg or platelet count >100,000). Surgery is limited by how much to resect in a cirrhotic liver with poor regenerative capacity (Child B/C) and multifocality. Thus resection is not encouraged for Child B/C cirrhosis with HCC [4]. Due to cadaveric organ shortage liver resection could be used as a bridge to transplantation [30]. Nowadays, the selection of candidates for resection has been refined and both the surgical technique and pre-existing imaging planning and immediate post-operative management have been optimized [10,31]. The perioperative mortality in most referral units for Child A cirrhosis with HCC is expected to be 2–3%, with blood transfusion requirements of less than 10% due to ultrasonic dissector, intermittent pringle manouevre and low central venous pressure maintenance. An overall 5-year survival of 60% is expected [4,28,29]. Disease-free survival is better after anatomical (5-year 63%) than non-anatomical resection (35%) (Figs. 2 and 3). There is a high risk of recurrence in the remnant liver distant from the resection margin. The pattern of recurrence influences subsequent therapy allocation and outcome [32–35]. The patient will be reassessed by BCLC staging and re-treated accordingly [26,29,32]. The operative mortality in the non-cirrhotic liver (FLC) is less than 2% and the 5-year survival following resection is 75%. It is unclear whether the histology alone, the absence of underlying chronic liver disease or the greater resectability rate account for the better prognosis of FLC [10].

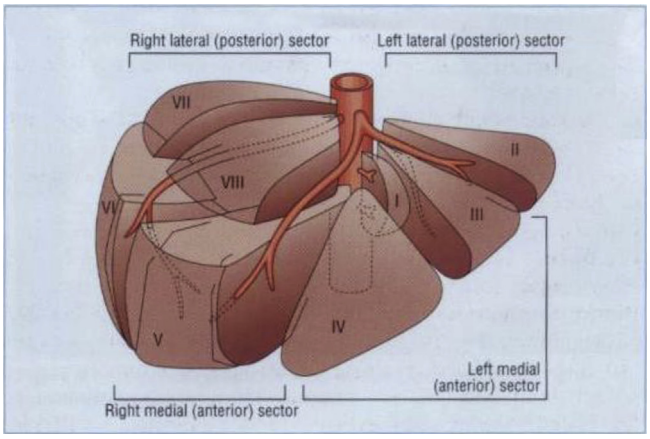

Fig. 2. Couinaud's segmental anatomy of the liver (with permission).

(b) Local therapy: if HCC is unresectable or not technically feasible due to local spread, alternative therapies such as radiofrequency ablation (RFA), percutaneous ethanol injection (PEI) which induce coagulative tumour necrosis and transarterial chemo-embolisation (TACE) are considered [36]. Percutaneous ablation (RFA, PEI) is the best treatment option for patients with early stage An HCC (BCLC staging) who are not suitable for resection or transplantation and in some Japanese centres this is offered as the first therapeutic option [26]. Complete ablation in more than 90% of cases with local recurrence rate of less than 1% for tumours less than 2 cm is reported [37]. RFA has a higher anticancer effect than PEI leading to a better local control of the disease as the energy generated eliminates small-undetected satellites in the peritumoral tissue. Thus PEI is recommended in the few cases where RFA is not technically feasible [10]. It is uncertain whether these local ablative techniques can be considered as competitive alternatives to resection [36].

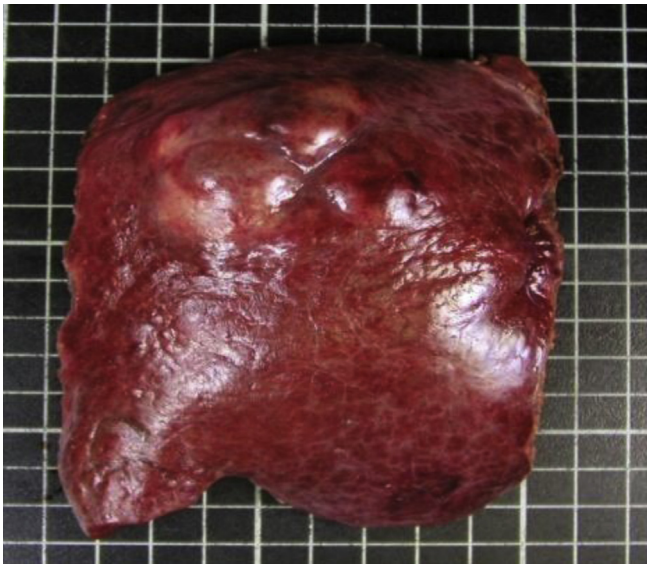

Fig. 3. Segmental liver resection.

TACE is a safe and effective measure for intermediate stage B (BCLC) and, controls tumour progression with a 40% response rate prior to liver transplantation for patients fulfilling Milan criteria [26,38]. The response rate to TACE may predict disease-free survival after liver transplantation [10,39].

(c) Liver transplantation: liver transplantation is the only hope for cure if tumour is small (<5 cm diameter) in a cirrhotic liver and considered to be the first line treatment option. It allows radical resection of tumour and treatment of underlying liver disease including Child B/C cirrhosis, if within Milan (or UCSF) criteria and no anaesthetic or surgical contraindications [7]. Limitations of liver transplantation apart from donor shortage include the risk of drop out while waiting (4% per month) and the perioperative mortality rate [6,7]. The operative mortality albeit low may arise from technical and infectious complications. The technical complications include haemorrhage, hepatic artery thrombosis, venous outflow obstruction, portal vein stenosis/thrombosis, bile leak, and biliary stricture. These may cause poor early graft function. Other shortcomings include rejection (hyperacute, acute cellular, or chronic) and disease recurrence. The latter may be a late cause of graft dysfunction. Improved results have emanated from better pre- and post transplant management, improved anaesthesia, innovative surgical strategies, early detection and treatment of infective complications and the further progress in immunosuppression [6]. Currently there is excellent long-term disease-free survival exceeding 70% at 5 years [30,40]. However, 30% of patients will exceed Milan criteria on histological examination of the explanted liver, and adverse histological features (multifocal disease, vascular invasion, and poorly differentiated tumours) carry a poor prognosis [41]. Pre-transplant tumour biopsy is recommended by a few centres in order to incorporate tumour histology into selection of patients for transplant in addition to size criteria [40,41].

Living donor transplantation of the right hepatic lobe is an alternative to the cadaveric organ shortage, but this approach is hindered by the risks of donor morbidity (20–40%) and mortality (0.3–0.5%). It would benefit patients with a lower expectancy, around 50% at 5 years and with thus a high risk of tumour progression if the waiting time is expected to be long [6]. Pre-transplant TACE or RFA is considered in borderline cases and like liver resection may be used as 'bridge' treatment if the predicted waiting time from listing to transplantation is more than 7 months [30]. This would reduce the risk of drop out of patients from the transplant waiting list (Fig 4). Neoadjuvant treatment to downstage patients beyond Milan criteria cannot be adopted as a tool to refine patient selection [42]. A caution in interpreting 'downstaging' of tumours is that the initial prognosis from the original histology as to the likelihood of putative/occult micrometastasis does not alter even if the therapy makes the primary tumour smaller. The optimization of modern immunosuppressive therapy such as FK506 (tacrolimus) and rapamycin has diminished the risks of rejection or recrudescence of HBV/HCV infection following liver transplantation [6].

2.3.2. Unresectable or metastatic disease

The breakthrough in the treatment of this complex disease is with molecular therapy such as Sorafenib (tyrosine kinase inhibitor) which is the standard systemic therapy for HCC. Sorafenib acting against vascular endothelial growth factor receptor 2, platelet-derived growth factor receptor and c-kit receptors induces a 31% decrease in the risk of death with a median survival of 10.7 months vs 7.9 months for placebo in patients with advanced

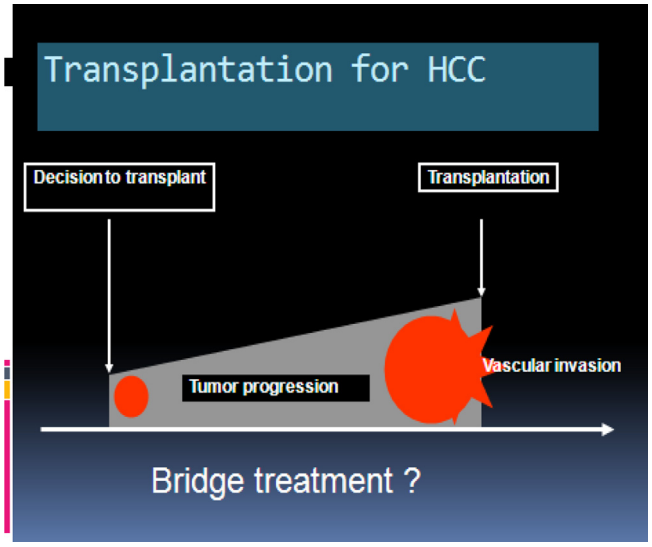

Fig. 4. 'Bridge' treatment prior to liver transplantation.

disease [43]. It is indicated for patients with well-preserved liver function (Child-Pugh A disease), with advanced tumours (BLCC stage C) or those patients who have failed TACE or other ablative therapy. Its role in an adjuvant setting is however currently unknown [44]. External beam radiation therapy has been of limited value since HCC is relatively radioresistant whereas the normal liver parenchyma is very radiosensitive. However, selective internal radiotherapy (SIRT) for inoperable HCC by injection of radioisotopes (Yttrium-90 bound to glass beads or resin) as microspheres into the hepatic artery offers the advantage of increased delivery of isotope within the tumour and decreased systemic toxicity. As the hepatic artery primarily provides the blood supply to HCC and portal vein to liver parenchyma, the mean cumulative radiation dose in the tumour has been shown to be 6240 cGy as compared to 555 cGy in the normal liver and 290 cGy in the lungs [45]. The limitations are that the tumour has to be hypervascular but devoid of arteriovenous shunts and to be of small size less than 5 cm if using low energy Iodine. An objective tumour response is observed in 40% of the patients, reduction in tumour size in 75% and complete necrosis for smaller lesions. This was associated with a 6 months survival rate of 48% as compared to 0% in a control group receiving only medical support [46]. The BCLC stage D patients with massive tumour burden, macroscopic invasion or extrahepatic spread and deeply impaired physical status (performance score >2), should receive symptomatic treatment that includes pain management, nutrition, and psychological support [4,10,26].

3. Prevention of HCC

Once cirrhosis is established, the benefits of antiviral therapy in preventing HCC development are not robustly demonstrated [4]. The inhibition of viral replication by lamivudine resulted in significant improvement in liver function in patients with decompensated HBV induced cirrhosis considered not to be candidates for liver transplantation [47]. Other nucleoside analogues under development may have therapeutic potency. Vaccination against hepatitis B virus is recommended to all newborns and high risk groups, although there is evidence that they have accelerated the accumulation of mutations [48]. DNA-based immunization may induce humoral and cellular responses with the potential to eradicate the virus [49]. Current public health measures for preventing HCV/HBV transmission including testing blood donors for hepatitis

B and C, needle exchange programmes, encouraging life styles that prevent alcohol abuse, and surveillance of high-risk individuals may see marked decline of the disease in future generations [50].

4. Conclusions

The future of hepatocellular carcinoma would still rely on prevention, effective treatment of the causative hepatitis B and C infections and surveillance of high-risk individuals for early diagnosis and management. There is the need for provision of therapy that is most appropriate for the stage of disease. A better understanding of molecular hepatocarcinogenesis may identify novel targets for oncogenic therapy.

Conflicts of interest

No conflicts of interest have been declared by the authors.

Funding

None.

Ethical approval

No ethical approval required for this publication.

Author contribution

EPW is the main author, GE made pathological research. MNN gave advice and performed some literature search. DSN did public health literature search.

Key learning points

- Fifth most common cancer world wide.
- 70–90% of HCC develop on a background of cirrhosis but Hepatitis B virus is directly oncogenic and can cause HCC in the absence of cirrhosis.
- Serum alpha-foeto protein is elevated in only 50–60% of cases but is useful as a baseline prior to treatment.
- Disease free survival is better after anatomical than non-anatomical resection (5 years survival 63% versus 35%).
- It is the small HCC in the setting of cirrhosis which is better treated by transplantation than resection.
- Excellent long term disease-free post-transplant survival if restricting patients to Milan or UCSF criteria.
- Tumor differentiation and vascular invasion are important predictors of survival after surgical resection or liver transplantation.
- Response rate to TACE may predict disease-free survival after liver transplantation.
- Need for provision of therapy that is most appropriate for the stage of the disease.
- The outcome of patients with HCC may remain poor because of late diagnosis.

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