1

The clinical management of hepatic neoplasms

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Introduction

The liver is the organ most frequently involved by cancer. In developing countries hepatocellular carcinoma is a major public health problem responsible for over 500 000 deaths per year [1]. In the West its incidence is rising, in part due to the increasing prevalence of chronic hepatitis C virus infection [2,3]. The liver is also the commonest site of metastases, and up to 75% of primary tumors drained by the portal venous system involve the liver before death.

This chapter will review the epidemiology, etiology, and current management of hepatocellular carcinoma and of secondary liver cancer, with particular reference to colorectal metastases as a paradigm for the multidisciplinary management of cancer.

Hepatocellular carcinoma

Epidemiology and etiology

Hepatocellular carcinoma (HCC) is one of the commonest malignancies worldwide but with wide geographical variation, the highest incidence occurring in sub-Saharan Africa and the Far East [1]. This variation suggests the importance of environmental factors (Table 1.1). Prime among these are chronic infection by hepatitis viruses B and C (HBV and HCV) and exposure to aflatoxin. In a study of 22 000 Chinese males, 15% of whom were HBV carriers, the relative risk for HCC development in HBV-positive men was 98.4 [4]. An HBV vaccination program, inoculating neonates, was initiated in Taiwan in the early 1980s and has resulted in a clear reduction in the incidence of childhood HCC [5]. However, an effect on the incidence of HCC in adults may take a further 20 years to become apparent. Evidence also suggests that genotype Ce is an important risk factor, and antiviral

Interventional Radiological Treatment of Liver Tumors, ed. Andy Adam and Peter R. Mueller.
Published by Cambridge University Press.

Table 1.1 Major risk factors for hepatocellular carcinoma

Chronic liver disease (usually at the stage of cirrhosis)
Chronic hepatitis B virus infection
Chronic hepatitis C virus infection
Dietary exposure to aflatoxin
Increasing age
Male gender

therapy in patients with chronic hepatitis B may also reduce the incidence of HCC [6,7]. The epidemiological evidence linking chronic HCV infection and HCC is similar to that for HBV. In a study of almost 10 000 Chinese males, 5% of whom were HCV-positive, the relative risk for HCC was 21.5 [8]. Although there is no vaccine against HCV there is increasing evidence that a sustained virological response to interferon or interferon/ribavirin decreases the risk of HCC development, while the 1b genotype increases it [9,10]. The great majority of HCCs arise in the setting of chronic liver disease, usually at the stage of cirrhosis, and all types of cirrhosis, particularly in males, are at a high risk of developing HCC [11].

Aflatoxin, produced by the fungus *Aspergillus flavus*, which grows on cereals stored in damp conditions, is one of the most potent liver carcinogens known, and a clear relationship between intake and incidence of HCC exists in high HCC incidence areas. As well as methods to improve grain storage to reduce aflatoxin exposure, the possibility of chemoprevention is an area of active research [12,13].

Diagnosis

The functional reserve of the liver is such that tumors can reach a considerable size before causing symptoms or signs, typically right upper quadrant pain, hepatomegaly, and weight loss. Decompensation of chronic liver disease (variceal hemorrhage, ascites, encephalopathy) is also a frequent presentation. Less commonly, a tumor may rupture, resulting in severe abdominal pain, shock, and hemoperitoneum [14]. Rarer presentations include hypoglycemia, hypercalcemia, and polycythemia due to tumor secretion of insulin-like growth factors, parathyroid-related hormones, and erythropoietin, respectively [15]. HCC is increasingly diagnosed pre-symptomatically as a result of screening programs.

Dynamic triphasic computed tomography (CT) or gadolinium-enhanced magnetic resonance imaging (MRI) will classically show marked enhancement in the

arterial phase with relative hypovascularity ("washout") in the portal or late phases. The European Association for the Study of the Liver (EASL) criteria state that in a patient with cirrhosis and a mass greater than 2 cm, this radiological appearance (confirmed by two imaging modalities) is diagnostic of HCC without the need for histology [16]. The presence of an enhancing liver mass on one imaging modality with a serum alpha-fetoprotein (AFP) level greater than 400 ng mL^{-1} is also considered diagnostic.

Cross-sectional imaging is required to stage the disease so that treatment can be planned. In particular, size, number, and distribution of tumors can be established, as well as the presence of macrovascular (portal vein) invasion and extra-hepatic disease. Although contrast-enhanced CT and MRI are the best current imaging modalities, both techniques may miss up to 30% of lesions (as detected in the explanted liver following liver transplantation), especially those less than 1 cm [17].

Serum AFP is elevated in 70% of patients with HCC [18]. It is of value in the diagnosis of HCC in patients with cirrhosis and has been used as a surveillance tool in high-risk populations. However, levels of 500 ng mL^{-1} or more can occur in benign liver diseases, notably chronic active hepatitis and fulminant liver failure. Nevertheless, a rising AFP is strongly suggestive of HCC. It may also be useful in monitoring the effects of treatment and for the detection of disease recurrence or progression following treatment.

For a liver mass not fulfilling the EASL criteria, a diagnosis of HCC requires histological confirmation. Fine-needle biopsy may be limited by sampling error, particularly for small lesions, and by difficulty in distinguishing well-differentiated HCC from dysplasia or adenoma. Some groups believe that biopsy may risk tumor seeding along the needle track and recommend avoidance of the procedure in candidates for surgical resection or transplantation. Histological type is not of prognostic significance, with the exception of the fibrolamellar variant, which typically occurs in younger patients without underlying chronic liver disease. In this setting, resection rates are higher and prognosis is better (median survival 5 years), although this may reflect the younger age and absence of cirrhosis [19].

Screening

Since HCC predominantly occurs on the background of chronic liver disease, usually at the stage of cirrhosis, this has a significant impact on the mode of presentation, complicates diagnosis, and limits therapeutic options. Thus, the identification of risk factors (Table 1.1), which may lead to interventions that

reduce its incidence and form the basis of screening programs for high-risk populations, is of particular importance. There is some evidence that this can reduce disease-specific mortality [20]. Current guidelines suggest that those in a high-risk group undergo 6-monthly ultrasound examinations. Serial AFP measurement has limited sensitivity, and whether or not it should be used as a part of a screening program remains controversial [21–23].

Staging and prognosis

For most cancers, prognosis is predominantly determined by tumor stage. However, HCCs usually occur on a background of cirrhosis, which independently contributes to prognosis [24]. For the majority of patients, prognosis is poor, with treatments other than surgery having little impact on survival. Tumor size is a key prognostic factor, with survival approaching 3 years for tumors less than 3 cm but only 3 months for those larger than 8 cm [25]. Vascular invasion increases with tumor size, but is an independent prognostic factor; even large tumors can have a good prognosis following surgical resection in the absence of vascular invasion [26,27]. Underlying cirrhosis may limit prognosis and can influence treatment options such as surgical resection and chemoembolization, which require sufficient hepatic reserve to be performed safely. Prognostic models for HCC are therefore complex and should take into account tumor stage, degree of liver impairment, patient fitness, and treatment efficacy.

Treatment options for HCC

Liver resection

The ability to resect a tumor depends on its size, location, relation to blood vessels, and underlying liver function. In patients without cirrhosis, up to 75% of the liver can be removed safely, and hepatic resection is the treatment of choice. Resection in patients with cirrhosis is still associated with significant morbidity and mortality, although this has fallen to less than 5% with recognition of the segmental anatomy of the liver, improvements in surgical technique and postoperative management, combined with better patient selection. Less than 20% of patients are suitable for resection, although this may increase as screening programs detect tumors at an earlier stage. Survival is better for solitary tumors less than 5 cm with negative resection margins and an absence of vascular invasion or lymph-node involvement, with 5-year survival up to 70% [28,29].

Table 1.2 Eligibility criteria for liver transplantation in patients with hepatocellular carcinoma

Milan criteria	UCSF criteria
One tumor < 5 cm *or* Up to 3 nodules, each ≤ 3 cm	One tumor < 6.5 cm *or* Up to 3 nodules, each ≤ 4.5 cm, and total tumor diameter ≤ 8 cm

Transplantation

Liver transplantation has the potential to treat both tumor and underlying cirrhosis, although patients with viral hepatitis have a risk of reinfection in the new liver. Assessment of tumor size and number, vascular involvement, and extrahepatic disease is essential to identify those patients most likely to benefit. In patients with no more than three tumors less than 5 cm, survival is similar to that of patients with benign end-stage liver disease, and, where available, transplantation is the treatment of choice for HCC in a cirrhotic liver. This experience has led to the development of the Milan criteria (Table 1.2) to guide the selection of patients for transplantation, which can lead to 5-year survival in excess of 70% [30]. Recent reports indicate that these criteria may be extended whilst retaining good outcomes (University of California San Francisco criteria, Table 1.2) [31].

A major limitation to transplantation is the supply of donor organs. This results in a period, of uncertain duration, between listing and transplantation, with the risk that the tumor will grow beyond the criteria for transplant [32]. Thus, scoring systems used to allocate donor organs are weighted to prioritize patients with HCC [33]. Drop-out (disease progression to a level at which transplantation is no longer appropriate whilst awaiting a donor liver) may be best reduced by increasing the number/availability of donor organs, and this may be helped by the use of living donors. Early data indicate similar results to those achieved with cadaveric organs if the Milan criteria are followed, with low mortality amongst donors [34].

Many centers employ treatments such as local ablation and chemoembolization (see below) to bridge the gap between listing and receipt of the transplant, although there are no prospective randomized data to indicate the utility of this strategy [35].

Local ablation

Ablative therapies, including percutaneous ethanol injection and thermal ablation, appear, by many criteria, to be as effective as surgery in appropriately selected cases. Like surgery, however, they are less effective as tumor size increases, particularly beyond 5 cm. As well as increasing difficulty in achieving complete ablation, this probably reflects the fact that as tumors increase in size the frequency of vascular invasion increases and, with it, the likelihood of metastasis.

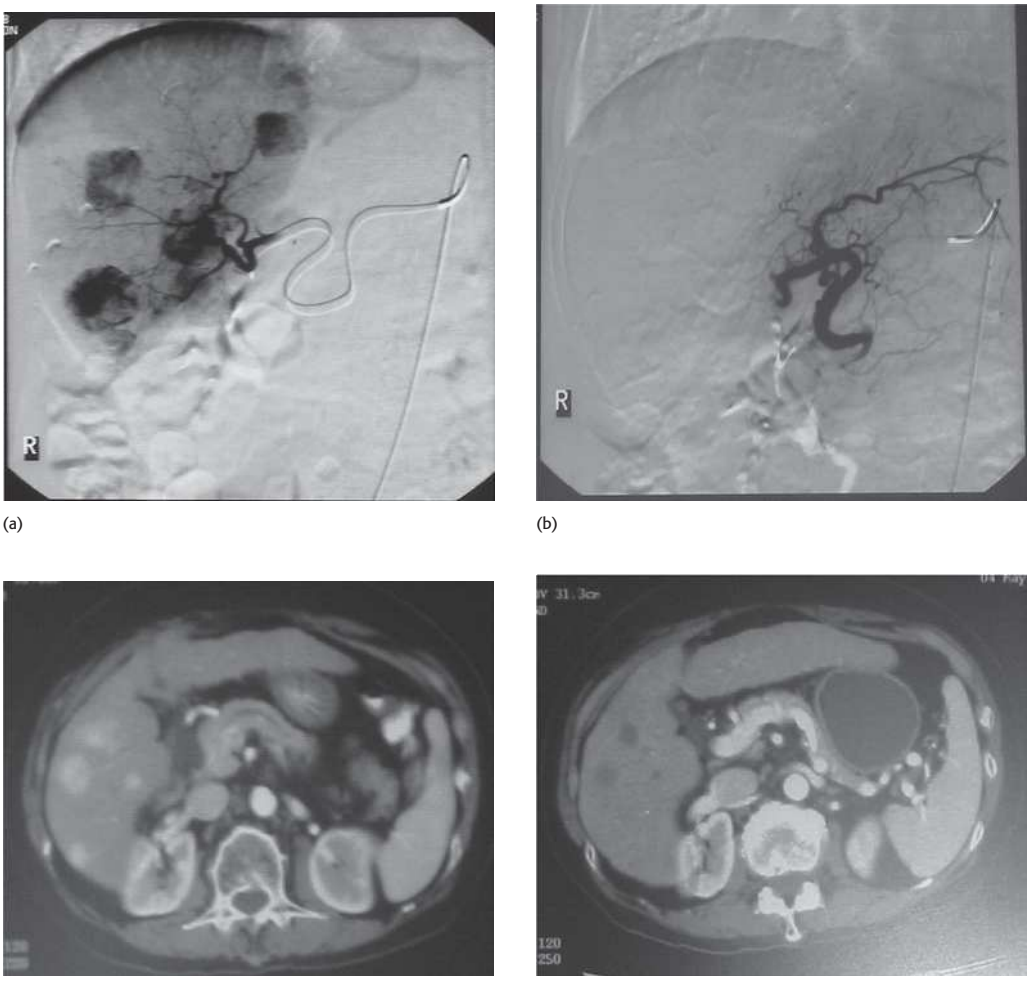
Treatment is usually performed percutaneously under image guidance. Several methods for tumor destruction have been used, the most widely studied being percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA). Injection of 90% ethanol under ultrasound guidance is technically straightforward, inexpensive, safe, and, depending on the severity of underlying cirrhosis, can result in 5-year survival of up to 50% [36]. Complete tumor necrosis is achieved in 70% of tumors less than 3 cm in diameter, but this falls with increasing size, probably due to the inability of the injected volume to disperse evenly throughout larger tumors.

Radiofrequency ablation is a localized thermal treatment producing tumor destruction by heating a probe inserted into the tumor to temperatures exceeding 60 °C, which can be performed percutaneously under image guidance, laparoscopically, or at laparotomy. The procedure is of limited applicability for subcapsular lesions, and when a large blood vessel is nearby it is difficult to obtain sufficiently high temperatures for complete tumor necrosis because of the heat-sink effect.

Randomized studies have compared RFA with PEI. A study in patients with tumors up to 4 cm demonstrated that RFA was superior in terms of tumor necrosis and survival, with 3-year survival of 74% versus 51% [37]. Further studies have demonstrated similar advantages for RFA in treating smaller tumors [38,39]. In general, RFA was associated with fewer sessions to achieve complete tumor necrosis, with no significant differences in morbidity and a likely improvement in survival.

Transarterial chemoembolization

HCC is a highly vascularized tumor, mostly via the hepatic artery. In contrast, nontumorous liver parenchyma derives most of its blood supply from the portal vein. Thus, transarterial chemoembolization (TACE) utilizes selective catheterization of the hepatic artery to deliver regional chemotherapy and embolize tumor-feeding arteries (Fig. 1.1). Chemotherapy is first injected, often mixed with lipiodol, an oily compound that accumulates preferentially in tumors, probably via enhanced permeability of



(a) (b)

(c) (d)

Figure 1.1 Transarterial chemoembolization. (a, b) Hepatic arterial angiography. (c, d) Contrast-enhanced CT. Pre-embolization (a and c) demonstrating hypervascular multifocal HCC. Post-embolization (b and d) showing tumor circulation abolished. *See color plate section*.

leaky tumor vasculature and retention due to impaired lymphatic drainage, with the aim of retaining the chemotherapy to increase tumor concentration and reduce systemic exposure. This is followed by embolization of tumor-feeding arteries using one of a variety of embolic materials [40,41]. For chemoembolization to be performed safely, there must be adequate blood supply to the non-tumorous liver via the portal vein, and it is therefore contraindicated in the presence of main portal vein

thrombosis. Other contraindications include extrahepatic disease, advanced cirrhosis, and poor performance status. Embolization is frequently complicated by a characteristic syndrome of abdominal pain, fever, and nausea, which is normally self-limiting within 2–4 days, although occasionally patients go on to develop liver abscess [42].

Two recent randomized controlled trials and a meta-analysis have demonstrated a survival benefit for patients receiving TACE compared with supportive care [43–45]. The general applicability of these data is limited by the relatively small sample size, and by the heterogeneity of the patient populations and the techniques used, with differences in the choice of chemotherapeutic agent, embolic agent, and use of lipiodol. Nevertheless, the key to successful chemoembolization is undoubtedly patient selection, and both the positive trials suggest the ideal candidate has well-preserved liver function and asymptomatic disease.

A major limitation of locoregional approaches is disease recurrence, which may represent the growth of pre-existing micrometastases from the primary tumor or the development of a new tumor, considered, arbitrarily, to have occurred when tumor develops more than 3 years after treatment. Since local recurrence may reflect pre-existing micrometastases in the immediate vicinity of the primary tumor, the ability of RFA to achieve a wider margin may explain its superiority to PEI.

In the absence of an effective systemic agent, there are no conclusive data that adjuvant treatment can decrease the risk of tumor recurrence.

Systemic therapies for HCC

The majority of patients with HCC have multifocal disease, bilobar disease, extrahepatic disease, and/or underlying cirrhosis, such that surgery, ablation, or chemoembolization are not indicated. For these patients, systemic therapy is required.

Chemotherapy

Objective radiological response rates for single-agent chemotherapy are low. The most widely used drug has been doxorubicin, although systematic reviews of randomized trials have failed to discern a significant survival benefit [46]. Combination chemotherapy can induce higher response rates in the range of 20–30%, but with no evidence of a significant impact on survival [47].

Interpretation of the impact of chemotherapy is limited by the small size of clinical trials and the heterogenous patient groups. More recently, a large-scale trial has investigated the novel thymidylate synthase inhibitor nolatrexed, using

doxorubicin as the comparator. Despite encouraging evidence of activity in earlier-phase trials, in fact patients receiving nolatrexed survived for a significantly shorter time than those in the control arm (4.7 compared to 6.9 months, $p = 0.0068$). Whilst the statistical assumptions used in the design of this trial were based on demonstrating superiority for nolatrexed, since there were no obvious nolatrexed-related early deaths some have argued that this study provides evidence that doxorubicin may, in fact, positively influence survival in appropriately selected patients [48]. Nevertheless, whilst conventional cytotoxic therapy has undoubted activity against HCC, whether or not this translates into a survival advantage has still not been rigorously demonstrated [49].

Endocrine therapies have been investigated in HCC based on reports of estrogen receptor expression in some cases. Early small studies with anti-estrogenic and anti-androgenic agents showed promise [50]. However, large prospective controlled studies have refuted any role for hormonal agents including tamoxifen [51].

Octreotide, a somatostatin analogue used to treat carcinoid tumors by suppressing the secretion of peptide hormones, has been tested in HCC based on proposed suppression of tropic hormones (insulin and insulin-like growth factors), anti-angiogenic activity, and presence of somatostatin receptors on HCC [52,53]. However, whilst an initial small study suggested promising activity, this has not been corroborated in subsequent larger randomized trials [54–56].

Angiogenesis and hepatocellular carcinoma

As a tumor grows to exceed the size at which oxygen enters by diffusion, development of a blood supply is essential. Vascular endothelial growth factor (VEGF) is a key signaling protein involved in angiogenesis, acting predominantly on vascular endothelial cells via VEGF receptor 2. VEGF production is stimulated by hypoxia, and circulating VEGF then binds to its receptors on endothelial cells, triggering a tyrosine kinase signaling cascade leading to upregulation of genes that promote angiogenesis. In HCC there is overexpression of VEGF, which appears to correlate with the degree of differentiation and tumor size [57,58]. Angiogenesis can be inhibited pharmacologically either by small molecule inhibitors of VEGF receptor signaling (e.g., sorafenib) or through a monoclonal antibody targeted against VEGF preventing its interaction with receptors (e.g., bevacizumab). Both approaches have entered clinical trials in patients with HCC.

Sorafenib

Sorafenib is an oral multikinase inhibitor that targets the Raf/MEK/ERK growth-factor signaling pathway, which has increased activity in HCC [59]. A molecular abnormality common to many human cancers, including HCC, is abnormal growth-factor receptor signaling such that growth signals may be constitutively activated independently of the growth factor itself, resulting in uncontrolled cell proliferation and survival. In the active form, growth-factor receptors stimulate a signaling cascade in the cell cytoplasm whereby a series of enzymes is activated, often by phosphorylation. This cascade allows amplification and diversification of the signal. The Raf/MEK/ERK signaling pathway is one of those downstream of growth-factor receptors, and thus its inhibition may inhibit the deregulated growth of malignant cells (Fig. 1.2).

Sorafenib also targets VEGF receptor tyrosine kinases. Thus, sorafenib has direct anti-tumor and anti-angiogenic properties. In a phase II study, whilst the objective

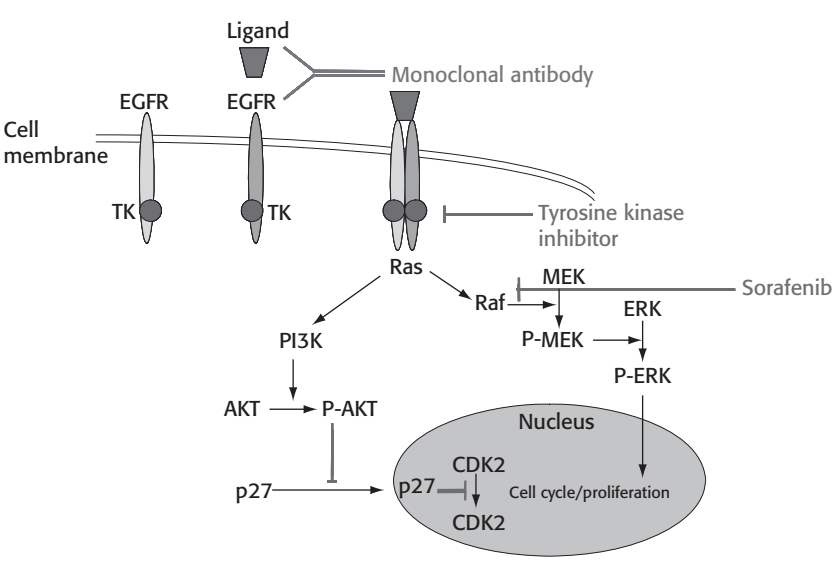


Figure 1.2 Cell signaling cascade following EGFR activation. Heterodimerization of EGFR with other HER receptors activates Ras, which activates PI3K to promote phosphorylation of AKT. Phosphorylated AKT inhibits nuclear translocation of p27, resulting in the loss of its inhibitory effect on cyclin dependent kinase 2 (CDK2). This allows CDK2 to promote entry into cell cycle with resultant cell proliferation. This growth stimulatory pathway can be inhibited at the level of the EGFR receptor (e.g., cetuximab), by inhibition of EGF receptor tyrosine kinase activity (e.g., erlotinib), or by inhibitors acting downstream of Akt (e.g., m-Tor inhibitors). Ras also activates the Raf/MEK/ERK pathway to promote cell proliferation, a process that can be inhibited by sorafenib.