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Review article

Future perspectives for hepatocellular carcinoma

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Background

Five facets of hepatocellular carcinoma (HCC) are identified that impact on future directions in the management of the disease: epidemiology, prevention, screening, diagnosis and therapy. Recent papers on HCC have been reviewed, and predictions have been made on developments in HCC over the next decade.

Discussion

It is predicted that hepatitis B-related HCC will decrease with vaccination, while hepatitis C-related HCC will become an increasing problem. Antiviral treatment and chemopreventive agents will prevent HCC development. Whole-population screening will not be an option, but screening is justified for individuals who can pay for it. There will be more emphasis on the use of tumour markers. Transabdominal ultrasound and triphasic spiral computed tomography will remain important radiological imaging techniques. The results of liver resection will not improve unless neoadjuvant/adjuvant therapy is proven to be effective. More patients with initially unresectable HCC will be down-staged to become resectable with improvements in local, regional and systemic therapies. Liver transplantation will be increasingly used. Local ablative therapy will improve the quality of survival but will have no impact on overall survival compared with surgical resection. The author hopes to review the accuracy of these predictions in 2013.

Keywords

hepatocellular carcinoma, screening, viral hepatitis

Introduction

Much of the progress in the developing field of hepatocellular carcinoma (HCC) depends on general progress in oncology, on many non-cancer-related areas such as antiviral therapeutics and treatment of chronic liver disease, and on public health initiatives. It would therefore be inappropriate to make predictions in this field for the very near future, i.e. the next 1–2 years, and it would be difficult for the distant future of 100 years and beyond. The aim of this article is to survey the current status of the field and, on the basis of current knowledge, to make predictions for the next decade. Five facets of HCC are identified that impact on future directions in the management of the disease: epidemiology, prevention, screening, diagnosis and therapy.

Epidemiology

HCC is one of the commonest internal malignancies worldwide, with an occurrence of at least 1 million new cases annually. It is the seventh most frequent malignant tumour in men and the ninth most frequent in women. The outcome of HCC is uniformly poor in most countries, with the overwhelming majority of patients dying in a few weeks, or at best, in months; the death toll from this disease is considerable [1]. The strikingly uneven geographic distribution of HCC is closely related to environmental agents, particularly hepatitis B virus (HBV). Other aetiological agents that have been found to be associated with HCC are hepatitis C virus (HCV), aflatoxins, microcystin from blue-green algae, chronic alcoholism, hereditary liver diseases and any other condition that causes cirrhosis.

Prevention

Of the many preventive measures in HCC, the most important development is in areas related to carcinomas that complicate HBV and HCV infection and aflatoxin exposure. Vaccination is the most practical and cost-effective way of preventing HBV-related HCC. A universal vaccination programme in Taiwan started in 1984 has shown a decreasing hepatitis B surface antigen carrier rate from 10% to 1.3% at 10 years after immunisation [2], and a significant decrease in incidence

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of HCC in boys 16 years after immunisation [3]. It has been predicted by Chen and his associates that HBV-related chronic hepatitis will significantly decrease in Taiwan by 2015 and HBV-related cirrhosis and HCC by 2040 [4]. However, the success of vaccination in many parts of the world is still limited by the lack of political will. Although vaccination for HBV is cheap and effective, a universal vaccination programme is now practised in only a few countries. Also, the development of mutant viruses with the capacity to escape the protection of vaccination can further limit the success of vaccination. Unfortunately, there is currently no vaccine for HCV.

Treatment of chronic hepatitis

There is emerging evidence that treatment of chronic viral hepatitis dramatically and coincidentally decreases the incidence of HCC. Two agents are available for the treatment of chronic hepatitis B: interferon-alpha and lamivudine. Both agents are associated with important limitations of efficacy or safety, or both. These limitations and other problems associated with the evaluation of current and investigational therapies for chronic hepatitis B infection give rise to several key issues in management of HBV: duration of therapy, goals of therapy, need for standardisation of the measurement of clinical responses and definition of response to therapy [5].

The first approved therapy for HCV infection was recombinant interferon. Subsequently, controlled studies demonstrated that the combination of interferon-alpha and ribavirin leads to higher virological sustained responses in patients with chronic hepatitis C infection. A novel modification of the interferon molecule resulted in the formulation of pegylated interferons, which have a longer half-life than standard interferon. Recent trials have established the superiority of pegylated interferons compared with interferon-alpha in inducing sustained virological responses in patients with chronic HCV infection, with or without cirrhosis [6].

Nishiguchi and his associates studied the role of interferon-alpha in patients with chronic HCV infection in a prospective randomised controlled trial (RCT). They showed clearly that viral replication could be inhibited in many subjects, and the group receiving interferon-alpha had a decreased incidence of HCC [7].

Chemoprevention

In a small RCT, Muto and colleagues showed that oral supplementation of an acyclic retinoid prevented the occurrence of a second primary HCC after curative treatment of the initial tumour with resection or local ablative therapy [8], indicating that chemoprevention is effective in hepatitis-related HCC.

A clear correlation between aflatoxin and the development of HCC has been established. Aflatoxin is activated in the liver to a carcinogenic metabolite that causes HCC. The drug oltipraz can stimulate a detoxification pathway by inducing the effects of gluthathione-S-transferases to form an inactive and non-carcinogenic metabolite from aflatoxin, which is excreted through the biliary system. It has already been shown in animal studies that the administration of oltipraz can almost completely abolish the carcinogenic effects of aflatoxin. Field trials of this drug are now underway in China, and the results are promising [9].

Avoidance of carcinogens in food and drinking water

Of the vast arrays of possible carcinogens in foodstuffs and drinking water, aflatoxin remains the most important. The fungi *Aspergillus flavus* and *A. parasiticus* produce two groups of aflatoxins, designated B_1 and B_2, G_1 and G_2 because of their blue or yellow-green autofluorescence. Aflatoxin B_1 is the most hepatotoxic, although to be carcinogenic it appears that chronic exposure to the mycotoxin is necessary [1]. The fungi grow readily on grains, peanuts and food products in the humid tropical and subtropical regions. Improvements in food storage and refrigeration have now cut down on food spoilage and contamination by these fungi.

Epidemiological studies in China have shown that people who drink pond-ditch water contaminated with the blue-green algal toxin microcystin have a high incidence of HCC [1]. The provision of good quality drinking water will cut down on HCC caused by microcystin.

Prevention of spread of hepatitis through body fluids

The routine screening of all blood products for HBV and HCV, the use of disposable needles and intravenous sets, and the emphasis on safe sex with condoms now emphasised in many countries are doubtless important in limiting the spread of hepatitis and decreasing the incidence of HCC.

Table 1. *Screening for HCC: criteria for a good screening programme*

Criterion	HCC
High prevalence	Yes in endemic areas
High risk groups	HBV, HCV hepatitis
High lifetime risks	10–40%
Disease lethal	Survival months, if not weeks if untreated
Availability of good screening tests	Alpha-fetoprotein, ultrasound
Availability of confirmatory tests	Serological, radiological and histological tests
Availability of curative treatment	Local ablative therapy, liver resection, liver transplantation
Low curative rate if symptomatic	Curative treatment possible in 10–30% of patients when symptomatic

Predictions on the incidence and prevention of HCC in next 10 years

- Worldwide there will be a steady decrease in HBV-related HCC.
- Hepatitis B immunisation will be effective, in spite of the increasing problem of mutant escape viruses.
- Hepatitis C will become an increasing problem.
- The disparity in incidence between East and West will fall.
- No vaccine will become available for hepatitis C within the next decade.
- Antiviral treatment and chemopreventive agents will prevent HCC development.

Screening for HCC

HCC satisfies almost all criteria for a good screening programme (Table 1). Screening for HCC has been shown to be effective in achieving a high liver resection rate of 70–90%, a low operative mortality rate of 0–2% and a good 5-year survival rate of 70–80% [10]. Why then is whole-population screening not adopted by countries with a high prevalence of HCC?

There are many reasons why a screening programme when applied to a population would fail and only a small percentage of the total cases screened would be successfully detected and treated [11]. At the level of the individual patient, the patient's condition or the liver function may be too poor, or the tumour may be too advanced to be cured at the time of diagnosis by screening. Even if the lesion can be treated with a procedure with curative intent, the tumour may recur or the patient may die as a result of a complication of the treatment. At the level of the population, screening can fail because some individuals at high risk of HCC may decline screening. For those on regular screening, some may decline regular follow-up. For those who have the tumour detected on screening, some may decline definitive treatment. Also progressive cirrhosis, liver failure and complications of portal hypertension may account for additional patients dropping out of the screening programme.

Furthermore, a screening programme is expensive. Money has to be spent to set up an infrastructure for the screening programme, and a preliminary screen has to be done to detect individuals who are at high risk of developing HCC. Patients who are screened positive for HCC need further investigation, with many individuals ultimately proving incurable for the reasons listed above. Also, newly detected carriers of viral hepatitis would ask for medical treatment including antiviral therapy, which is expensive. The cost for screening for HCC in high risk patients in 1996 was estimated to be US$11 800–25 000 per tumour detected and US$26 000–113 000 per additional year of life gained [12, 13]. Thus whole-population screening is almost certainly not an option for most governments that have to set priorities in their health care expenditure.

On the other hand, screening in individuals who can pay for it produces good results. Bolondi and co-workers reported that screening did not increase the percentage of patients who underwent surgical resection or transplantation, but that 3-year survival and median survival increased in patients whose tumours were found at screening compared with those in whom HCC was found by chance [13]. Farinati and Gianni found that screening increased the percentage of patients who were eligible for transplantation (39% vs 26%) and increased the 4-year survival (50% vs 22%) and median survival (24 months vs 8 months) compared with patients in whom HCC was discovered by chance [14]. Tong and associates reported that of 173 patients with cirrhosis resulting from chronic viral hepatitis, 31 patients with HCC were detected by screening. Four of the 31 patients underwent liver resection, 8 underwent transplantation and 9 received

palliative treatment [15]. McMahon and colleagues demonstrated that screening for HCC in native Alaskans with chronic HBV led to improved resectability and 5- and 10-year survival rates [16]. Sherman and associates found that screening chronic carriers of HBV for HCC resulted in a liver resection rate of 50%, although only 40% of these patients survived for more than 2 years [17].

Predictions on screening

- Whole-population screening is almost certainly not an option as it is very expensive.
- Attempts to justify screening for a high risk group in a population will fail to show cost- or utility-benefit.
- Screening is justified in individuals who can pay for it.

Diagnosis of HCC

The diagnosis of HCC is established serologically (using tumour markers), radiologically, cytologically or histologically, either alone or in combination. Many tumour markers are currently in use for HCC (Box 1). Of these, alpha-fetoprotein (AFP) is most commonly used for HCC in diagnosis, in monitoring response to treatment and in prognosis.

Box 1. Tumour markers for HCC

- Alpha-fetoprotein
- Ferritin
- γ-Glutamyltranspeptidase isoenzyme
- Alkaline phosphatase
- Des-γ-carboxy prothrombin
- α-1-Antitrypsin
- Aldolase A
- 5′-Nucleotide phosphodiesterase V
- Tissue polypeptide antigen
- α-L-Fucosidase

HCC-specific AFP isoforms have been identified by isoelectric focusing. The specificity of these AFP isoforms was assessed in a study on 53 patients who attended an outpatient clinic for chronic liver disease [18]. All 53 patients had AFP levels >50 ng/ml, and there was no radiological evidence of HCC at entry into the study. The HCC-specific AFP (+II) was detected in the sera from 26 patients taken at the time of enrolment. During an 18-month follow-up (median 12 months) a diagnosis of HCC was established in 19 of the 26 patients. On the other hand, among those 27 patients without the HCC-specific isoform at entry into the study, only three developed HCC within the follow-up period. This study showed that HCC-specific AFP may permit malignant change to be inferred in patients with chronic liver disease before it becomes detectable radiologically.

The commonly used diagnostic imaging techniques in HCC are listed in Box 2. Transabdominal ultrasound scanning is commonly used for screening, for initial radiological assessment of the patient and for follow-up assessment. Triphasic spiral computed tomography (CT) is commonly used for accurate assessment of the location and extent of the disease.

Box 2. Diagnostic imaging for HCC

Ultrasound:
- transabdominal
- Doppler
- contrast-enhanced with intra-arterial CO_2 microbubbles
- colour Doppler enhanced with intravenous Levovist
- intra-operative
- laparoscopic

Computed tomography (CT):
- triphasic spiral
- arteriography
- arterial portography

Magnetic resonance
Hepatic angiography
Positron emission tomography
Single photon emission CT

Although there is still some controversy as to whether liver biopsy should be carried out before liver resection for resectable lesions, most liver surgeons would agree that preoperative liver biopsy is unnecessary unless the biopsy result would alter the plan of management, as biopsy still carries a small but inherent risk of bleeding, tumour rupture and needle tract seeding.

Predictions on diagnosis of HCC

- There will be more emphasis on the use of tumour markers in HCC in diagnosis, in monitoring response to treatment and in prognosis.
- Transabdominal ultrasound scan and triphasic spiral

CT will remain important radiological imaging techniques.

- The need for image-guided biopsy will decrease as serological and radiological techniques become refined.

Therapy of HCC

There are many treatment options for HCC (Box 3).

Box 3. Treatment options for HCC

- Liver resection
  - Partial hepatectomy
  - Orthotopic liver transplantation
    - Cadaveric
    - Living-donor (LDLT)
- Local ablative therapy
  - Injection of cytotoxic agent, e.g. ethanol
  - Application of an energy source, e.g. radiofrequency
- Hepatic artery transcatheter treatment
  - Transarterial chemoembolisation (TACE)
  - Transarterial radioembolisation (TARE)
- Systemic therapy
  - Chemotherapy
  - Immunotherapy
  - Chemo-immunotherapy
  - Hormonal therapy
  - Somatostatin analogue
- Other treatments
  - Gene therapy
  - Supportive therapy

Partial hepatectomy

Partial hepatectomy is still the treatment of choice for patients with good liver function and good general condition. It has the potential for 'cure'. The operative mortality rate nowadays approaches 0% for non-cirrhotic liver resection and <5% for cirrhotic liver resection. Unfortunately, only about 10–30% of patients have resectable HCC at the time of diagnosis [19]. For major liver resection, the portal vein supplying the lobe of liver containing the tumour can be embolised. This manoeuvre allows compensatory hypertrophy of the non-involved liver, making subsequent liver resection safer [20]. The 5-year survival after 'curative' partial hepatectomy ranges from 26% to 50%, with a mean of 30% [19]. The main cause of postoperative death (50–90%) is recurrent disease, and intrahepatic tumour is the commonest form of recurrence. It is generally believed that recurrences arise not because of inadequate resection but because of pre-existing microscopic tumour foci that are undetected by imaging, or because malignant cells have been disseminated during surgical manipulation. Thus, any neoadjuvant or adjuvant therapy that can decrease or delay the incidence of intrahepatic recurrence should improve the results of partial hepatectomy [19, 21]. Schwartz and associates undertook a systematic review of RCTs on neoadjuvant/adjuvant therapy for HCC and identified 13 studies with a patient follow-up beyond 3 years [21]. In 10 studies, neoadjuvant/adjuvant therapy had no impact on overall survival when compared to untreated controls. However, significant improvement in overall survival was shown in three studies, indicating that there may indeed be a place for neoadjuvant/adjuvant therapy after 'curative' liver resection.

Liver transplantation

Liver transplantation is the treatment of choice for patients with early HCC and decompensated cirrhosis. Liver transplantation has the following advantages over liver resection in the treatment of HCC: 1) it replaces a cirrhotic liver with a normal liver, 2) it prevents the onset of metachronous tumour in a cirrhotic liver and 3) it cures portal hypertension and its complications. The reported 5-year survival rate of liver transplantation for HCC approaches 50% [22]. In patients with a single tumour <5 cm, or with multiple tumours <3 in number and each <3 cm in diameter (the Milan criteria) [23], the results of liver transplantation for HCC can be as good as those carried out for end-stage liver disease without HCC, with a 5-year survival of >70% [22, 23].

In recent years, there has been an increasing interest in adult living-donor liver transplantation (LDLT) for hepatocellular carcinoma. The increase in the demand for cadaveric liver donation has led to an increased waiting time for liver transplantation and a drop-out rate from the transplant programme for patients with progressive HCC. The advantages of LDLT are better overall status of the recipient, better liver function of the graft and a shorter waiting time to transplantation, thus eliminating the need for neoadjuvant therapy. Moreover, recipients who do not meet the restricted transplant criteria in the transplant centres can be

transplanted. The results of LDLT performed exceeding the Milian criteria are encouraging, and 5-year survival rates of 25–44% have been reported [22]. The prediction must be that liver transplantation will play a more important role in the treatment of HCC.

Local ablative therapy

Of the many forms of local ablative therapy, percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) are those most commonly used. Local ablative therapy has the potential to 'cure' patients with a small HCC. When compared with other forms of curative therapy like partial hepatectomy or liver transplantation, it has the advantages of being minimally invasive and safe. It also causes little damage to the surrounding liver parenchyma and has few side effects.

Non-randomised studies have shown that PEI gives a good 3-year survival rate of 46–77%. However, post-treatment recurrence within the liver is high and is in the range of >50% in 2 years [24]. Two RCTs have been done: one trial evaluated PEI against no treatment [25], and the other evaluated PEI plus transarterial chemoembolisation (TACE) against TACE alone [26]. Neither study showed any impact of PEI on patient survival, although in each case PEI was used for patients with large HCCs, which are usually considered unsuitable. A meta-analysis combining these two RCTs showed that no firm conclusion can be drawn for the value of PEI [27].

RFA for small HCCs has received a good deal of attention recently. Good results have been achieved in non-randomised studies, with a complete tumour necrosis rate of 90–100%, and a local recurrence rate of 3.6% at a median follow-up of 19 months [24]. Non-randomised studies have also shown RFA to be better than PEI in achieving a higher complete tumour necrosis rate with fewer treatment sessions. The advantages of RFA over PEI were confirmed by an RCT [24], while another recent RCT even showed that significantly better overall survival can be achieved in patients treated with RFA compared with PEI [28]. Thus, RFA will gradually take over from PEI in the treatment of HCC for patients who are suitable for treatment with local ablative therapy.

Transarterial Chemoembolisation (TACE)

The term TACE has been used indiscriminately to describe a treatment procedure using the transhepatic arterial route to inject chemotherapeutic and embolising agents in the treatment of liver cancer. There has been no standardised protocol in the choice of chemotherapeutic agents, the dosage, the dilution, the rate of injection or the time interval between the treatments. Similarly, there is no agreement on the choice of embolising agent, the degree of embolisation and whether the chemotherapeutic agent should be given together with, or before, the embolising agent [19].

Non-randomised studies showed encouraging results with TACE in unresectable HCC [19]. Five RCTs have been published comparing some forms of TACE to supportive care [29–33], but only two showed that TACE conveyed a survival benefit [32, 33]. These studies emphasised the importance of using stricter criteria in the selection of patients for TACE before patients can benefit from the treatment. Patients should not have advanced HCC, there should be no major portal vein invasion and the liver function should be preserved. Also, the data from these studies stress the importance of the technique employed to perform TACE, the timing and the number of TACE procedures. A recent systematic review of RCTs revealed that TACE improves survival of patients with unresectable HCC [34]. TACE may become the standard therapy in selected patients.

An approach similar to TACE has been exploited by administering a therapeutic dose of radioisotopes into the hepatic artery, thereby irradiating the tumour internally while sparing the non-tumorous liver. Transarterial radioembolisation (TARE) for HCC has been used with iodine^{131}-lipiodol and yttrium^{90} microspheres. The results with non-randomised studies using iodine^{131}-lipiodol have been encouraging. The treatment has been found to be safe and effective in HCC [19]. In an RCT for HCC with portal vein tumour thrombosis, iodine^{131}-lipiodol was shown to improve survival compared with symptomatic treatment [35]. Yttrium^{90} microspheres have also been used in the treatment of HCC with good results. The treatment has been shown to be able to down-stage unresectable HCC to become resectable, while complete histological response of HCC to treatment has also been reported [36]. Unfortunately, no RCT has been carried out to compare yttrium^{90} microspheres with a control group of patients with symptomatic treatment.

Systemic therapy

The results of systemic therapy using chemotherapy,

immunotherapy, hormonal therapy or somatostatin analogue have been disappointing. A phase II study on the use of systemic chemoimmunotherapy with cisplatin, interferon-alpha, adriamycin and 5-fluorouracil showed promising results in unresectable HCC. The treatment gave an objective radiological response rate of 26%. For those who responded to the treatment, 18% were down-staged to become resectable and the 3-year survival after surgical operation was around 50%. Complete pathological response is possible with systemic therapy [37].

Gene therapy

Gene therapy is still at an embryonic stage. Anti-tumour strategies include the reintroduction of tumour suppressor genes into tumour cells, the expression of foreign enzymes to render tumours susceptible to treatment with chemotherapeutic agents and the enhancement of tumour immunogenicity by expressing immunomodulatory genes or by genetic vaccination with tumour antigens. Gene therapy may also be used for anti-angiogenesis to reduce tumour growth and metastatic potential. Other novel approaches aim at the development of genetically altered replication-competent viruses, which selectively replicate in tumour cells, inducing cell lysis [38].

Predictions on therapy

- The results of liver resection will not improve unless neoadjuvant/adjuvant therapy is proven to be effective.
- As local and systemic treatments improve, initially unresectable HCC will be down-staged to become resectable.
- Liver transplantation, especially LDLT, will be used increasingly.
- Local ablative therapy will demonstrate no or little impact on overall survival compared with liver resection, although the quality of life will be shown to improve.
- Neither new cytotoxic agents nor gene therapy will be shown to have an impact on overall survival of patients with HCC in the next decade; rather, any improvement in survival will be based on combinations of systemic therapy and locoregional therapy that are currently available.

Conclusions

I have made a number of predictions on five facets of HCC: epidemiology, prevention, screening, diagnosis and therapy. Some of these predictions will materialise, while others will not. I hope to have the opportunity to review the accuracy of my predictions in the year 2013.

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