Review-III

Hepatocellular Carcinoma

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SUMMARY

Hepatocellular carcinoma (HCC) is the fourth most common cancer worldwide. Over last two decades there is increased incidence rate and shift toward younger population. HCC is associated with conditions resulting in chronic liver injury. Malignant tumours of liver are primarily adenocarcinomas. Majority of the patients present with advanced disease. Imaging is required to assess operability. Standard treatment for operable tumour is partial hepatectomy or total hepatectomy with liver transplantation. Neoadjuvant chemotherapy; chemo-embolization or immunoembolization may make resection safer. Adjuvant chemotherapy or chemo-embolization has shown no benefit in terms of survival. Surveillance of high-risk population is a must for detection at early stages where curative therapy can be given. Patients with HCC who cannot undergo curative procedures are best treated in the setting of a clinical trial.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fourth most common cancer worldwide! Its incidence rate, however, has been increasing over the past two decades. In the United States, the incidence is 4.7/100,000.[2] In eastern Asia and middle Africa the incidence is more than five times that of North America. Furthermore, from 1981 to 1985 the peak incidence of HCC occurred in patients 80 to 84 years of age, whereas from 1991 to 1995 the peak was noted in persons 74 to 79 years of age. This shift in incidence toward younger persons seen over the last two decades coincides with the prevalence of the hepatitis C infection.[3,4]

ETIOLOGY

HCC is associated with conditions resulting in chronic liver injury (Table 1). Hepatitis B (HBV),[5,6] and hepatitis C virus (HCV)[7] infection appear to be the most significant causes of HCC worldwide, especially in patients with continuing antigenemia and chronic active hepatitis. The latent period between exposure to the hepatitis virus and the development of HCC varies between thirty to fIfty years. Unlike HBV; HCV associated HCC rarely occurs in carriers before the development of cirrhosis. The role of

Table I: Conditions Predisposing to or associated with development of Hepatocellular Carcinoma

INFECTIONS	ENVIRONMENT	METABOLIC DISEASES
Hepatitis B Virus	Androgenic steroid	Hemochromatosis
Hepatitis C VIrus	Aflatoxins	a_1-Antitrypsin deficiency
	Tobacco	Wilson's disease
CIRRHOSIS	N-nitrosylated compounds	Porphyria cutanea tarda
Alcohol	Pyrrolizidine alkaloids	Types 1 and 3 glycogen storage
Autoimmune hepatitis	Thorotrast	disease
Primary biliary cirrhosis		Galactosemia
Cryptogenic cirrhosis		Citrullinemia
		Hereditary tyrosinemia
		Familial cholestatic cirrhosis

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hepatitis B e antigen (HBeAg) and hepatitis B surface antigen (HBsAg) in the development of HCC was also evaluated.[8] The incidence rate was 1169/100,000 cases person-years among those positive for HBsAg and HBeAg, 324/100,000 person-years for those with HBsAg positive only, and 39/100,000 person-years who were negative for both. The relative risk for developing HCC was 60.2 (95% CI 35.5-102) among those positive for both HBeAg and HBsAg, compared with 9.6 (95% CI 6-15.2) among those who were negative for both. The authors concluded that the presence of HBeAg is associated with an increased risk of HCC, indicating that active replication of chronic HBV promotes carcinogenesis among those with chronic HBV infection. Additional risk factors for patients with HBV and HCV positivity are consumption of more than 80 grams of alcohol per day[9] and presence of HCC in a first degree relative.[10]

CHRONIC HEPATITIS IN INDIA

The incidence of HCC in India has been somewhat mysterious considering the high prevalence of HBV-related chronic liver disease. A meta-analysis[11] reported the prevalence of HBV infection in the general population to range from 1.1% to 12.2% with a mean of 3.34%. Thyagarajan et al indicates that there are wide variations in prevalence rates (based on HBsAg seropositivity) within the country. Within India there are zones of low, intermediate and high endemicity. Data from National Institute of Communicable Diseases showed the incidence of viral hepatitis to be about one per 1000 population. One ominous trend is the emerging rural endemicity. It is associated with age less than 20 years, male sex, poor socioeconomic status, illiteracy and history of injections. HCC is not a common cancer of the digestive tract in India and is much lower that in the Southeast Asian countries with 14120 new cases in 2001, which would be 1.6% of incident cancers.[13] Indian migrants also have lower incidence of HCC than migrants from Southeast Asia.

A high prevalence of HCV among acute (11 %) and chronic (25.3%) hepatitis patients with predominance of genotype 3.[4,15] HBV

genotypes also differ in their potential for causing disease. In a study of patients from Vellore,[16] genotype D, A and C were detected in 57.3%, 18% and 11.5% of patients with chronic hepatitis B. Patients with genotype C had a higher alanine transaminase levels which may predict a greater potential for symptomatic disease. In another study by Thakur et al,[17] genotype D was associated with more severe disease and predicted the occurrence of HCC in younger patients. Co-infection leads to higher than infection alone that is, HBV-9.1% and HCV-16.5%.[18]

Transfusion-associated hepatitis is a major problem in developing countries due to endemic hepatitis infections and lack of voluntary donors, trained personnel and funds. Prevalence of post-transfusion hepatitis B and C in India is about 1-5% and 1% respectively.[19]

PATHOLOGY

Malignant tumours of liver are primarily adenocarcinoma with two major cell types: hepatocellular and cholangiocarcinoma. Histologically, HCC is classified as: hepatocellular carcinoma (classical), hepatocellular carcinoma (fibrolamellar variant) (Table 2), cholangiocarcinoma (intrahepatic bile duct cancer), mixed hepatocellular cholangiocarcinoma and undifferentiated carcinoma. Biliary differentiation is associated with a poor outcome because these tumours are rapidly growing, less vascular and resistant to treatment.

HCC has been graded as well differentiated, moderately differentiated and poorly differentiated. No firm correlation between grade and prognosis has been established.

Three growth patterns that influence the resectability are -

- Hanging type of tumour, often resectable
- Pushing type, often encapsulated by a fibrous capsule. This variety too is often resectable
- Infiltrative type, often unresectable.

Table 2 : Comparison of standard Hepatocellular Carcinoma with the fibrolamellar variant

Characteristic	HCC	Fibrolamellar HCC
Male-female ratio	4:1-8:1	1:1
Median age	55	25
Tumour	Invasive	well circumscribed
Resectability	<25%	50-75%
Cirrhosis	90%	5%
AFP+	80%	5%
HepB+	65%	5%

AFP+, α -fetoprotein, HCC, hepatocellular carcinoma; HepB+, hepatitis B -positive.

STAGING

The American Joint Committee on Cancer (AJCC) has designated TNM staging for liver cancer (Table 3).

Table 3: TNM Staging

Primary tumour (T)

- TX: Primary tumour cannot be assessed.

- T0: No evidence of primary tumour.

- T1: Solitary tumour without vascular invasion.

- T2: Solitary tumour with vascular invasion or multiple tumours none more than 5 cm.

- T3: Multiple tumours more than 5 cm or tumour involving a major branch of portal or hepatic vein(s).

- T4: Tumour(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of the visceral peritoneum.

Regional lymph nodes (N)

- NX: Regional lymph nodes cannot be assessed.

- N0: No regionallymph node metastasis-.

- N1: Regional lymph node metastasis.

The regional lymph nodes include the hilar (in the hepato-duodenal ligament, hepatic and periportal nodes) and along the inferior vena cava, hepatic artery and portal vein.

Distant metastasis (M)

- MX: distant metastasis cannot be assessed.

- M0: No distant metastasis.

- M1: Distant metastasis.

AJCC stage groupings

Stage I   Tl, N0, M0

Stage II   T2, N0, M0

Stage IIIA   T3, N0, M0

Stage IIIB   T4, N0, M0.

Stage IIIC   Any T, Nl, M0

Stage IV   Any T, any N, M1

For the purpose of management, patients are grouped into:

- Localized, resectable (TI, T2, T3 and selected T4; N0, M0)

- Localized unresectable (Selected T2, T3 and T4; N0, M0)

- Advanced disease (any T, N1, M1).

CLINICAL PRESENTATION

Majority of the patients present with advanced disease because the liver is hidden behind the costal cartilages and due to its large functional reserve. Small tumours are often asymptomatic

and detected only incidentally, Vascular bruit is heard in 25% of cases.[20] Anorexia, nausea, lethargy and weight loss are common. The most common presentation is a triad of right upper quadrant pain, palpable mass and weight loss. Cirrhosis may be the first presentation, sometimes with hepatic decompensation (ascites, jaundice or encephalopathy). Because of its propensity for vascular invasion, hepatic failure may also occur due to portal vein thrombosis. Gastrointestinal bleeding often complicates the course and is the presenting symptom in 10% of cases.[21] It is associated with a poor prognosis. Jaundice, a presenting symptom in 50% of cases, may either be due to hepatic parenchymal insufficiency or biliary obstruction.[22,23] In less than 5% of cases, HCC can present as a paraneoplastic syndrome with hypercalcaemia, erythrocytosis, hypoglycemia and hypercholesterolemia.[24]

DIAGNOSIS

Diagnoses can be established by noninvasive investigations such as history, physical examination, blood tests and imaging. A liver mass consistent with HCC on computed tomography (CAT) or magnetic resonance imaging (MRI) and an alpha foetoprotein (AFP) of more than 500 ng/dl by radioimmunoassay (RIA) is usually sufficient for diagnosis. In such operable cases one should proceed for surgery without a biopsy. In case AFP levels are nondiagnostic or the patient is not a candidate for curative procedures, fine needle aspiration cytology (FNAC) is performed. This should be done only if the patient is suitable for palliative therapy, FNAC has yielded a higher percentage of accurate diagnosis as compared to needle biopsy, 86% versus 66%.[25] CAT or MRI and bone scan are required to look for metastasis to the lung, bone, peritoneum and adrenal gland.

PREOPERATIVE EVALUATION

Imaging is required to assess operability. CAT or MRI can sight the number and the distribution of tumours as well as degree of vascular invasion. Angiography in conjunction with helical CAT / MRI and MRI angiography provides information on the arterial anatomy and presence of tumour thrombi (in the hepatic veins, inferior vena cava or the portal vein), which can significantly alter the treatment approaches. Triple phase (noncontrast enhanced, arterial phase and portal phase) CAT images should be obtained as HCC is a very vascular tumour and images with contrast enhancement may be missed since they become isodense with the surrounding liver. Tumours are sometimes visible only during the noncontrast-enhanced phase. Hepatic angiography using lipoidal has the advantage of being preferentially retained in HCC because of the particle size. Laparoscopic evaluation may detect metastatic disease, bilobar disease, or inadequate liver remnant, and therefore obviate the need for open surgical exploration in doubtful cases.

Assessment of liver function tests and evaluation for cirrhosis (Table 4) is must. Patients older than 65 years or with symptoms associated with cardiopulmonary disease should be evaluated in detail. Cirrhotic liver have a reduced tendency to regenerate and are often associated with portal hypertension, both of which result in thrombocytopenia and deranged coagulation parameters. These can contribute to the increased risk of bleeding and liver failure after resection. The complication rate after ablative therapy also increases in proportionate to the degree of liver dysfunction.

A. MANAGEMENT OF OPERABLE HCC

SURGERY

Partial hepatectomy

This represents the most common potentially curable procedure for the treatment of HCC in patients without cirrhosis. Resection of localized liver cancer varies from segmental resection to trisegmental resection. Small margins are acceptable. A 5-year survival of 30-40% with median survivals approaching 3 years has been reported.[26] The major changes in operative conduct leading to an improved perioperative outcome include willingness for nonanatomic resection. Multiple tumours do not preclude surgical resection and have a 5-year

Table 4: Pugh's Modification of Child's Grading of Cirrhosis

Measurement	1 Point	2 Points	3 Points
Bilirubin (mg/dL)	1 -1.9	2 - 2.9	> 2.9
prothrombin time prolongation (sec)	1 - 3	4 - 6	> 6
Albumin (g/dl)	>3.5	2.8-3.4	<2.8
Ascites	None	Mild	Moderate to
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4

Note: Pugh-Child's grade A, 5 - 6 points; B, 7 - 9 points, C, 10 - 15 points.

survival between.24-28%.[26,27,28] An intraductal tumour presenting as obstructive jaundice[27] or synchronous direct invasion of adjacent organs such as diaphragm,[29,30] are not contraindication to surgery. One group that has particularly poor prognosis is patients with major intravascular extension. Cases with tumour thrombus in the portal vein or inferior vena cava are unlikely to have long term survival even after liver resection and thrombectomy.[31]

TOTAL HEPATECTOMY AND
LIVER TRANSPLANTATION

This approach allows for removal of the tumour with the widest possible margins. It results in removal of diseased parenchyma that may contain microscopic metastatic disease as well as parenchyma that may be predisposed to formation of second primary tumour. The best results are seen with the fibrolamellar variant. Features associated with poor long-term outcome include advanced stage, positive margins, tumour size more than 5 cm, multiple tumours, intravascular invasion, and bilobar disease.[32,33] Liver transplantation is associated with 10-20% of morbidity and mortality[34] though more recent series[35,36] have reported improved perioperative mortality. In patients with Pugh-Child grade B or C, this is the only potentially curative option. The greatest obstacle to liver transplantation is the limited availability of livers and cost of the procedure.

HEPATIC RESECTION (HR) VERSUS HEPATIC TRANSPLANT (HT)

The benefits of HT compared with HR in treating HCC with cirrhosis are controversial. There are no randomized trials comparing in early stage. Spain has the highest liver donation rate throughout the world (20 liver donors/10^6 inhabitants) and the proportion of dropouts (due to death or appearance of contraindications) is 15%. The encouraging survival data for HT (75% at 5 years) is due to a restrictive selection policy and a short waiting list. [37] The survival figures for HR from various series show a 5-year survival of 17%-53% and are composed of a heterogeneous mix of individuals in terms of hepatic function and stage.[38,39,40,41] Shabahang et al[42] showed that the results of both modalities are comparable in Child's A patients in terms of overall survival (66% vs. 57%) and disease free survival (66% vs. 36%). The group concludes that in Child's A patients HR is not only effective but is associated with quicker recovery, Llovett et al.[43] showed on an intent to treat analysis that the 1-.3- and 5- year survival was 84%, 69% and 69% for HT and 85%, 62% and 51% for HR. The 5-year survival of the best candidates (absence of clinically relevant portal hypertension) was 74% whereas it was 25% for the worst candidates (portal hypertension and bilirubin = 1 mg/dl). This group concluded that the outcome

Table 5: Comparison of various loco-regional therapies for HCC : advantages and disadvantages

Treatment	Advantages	Disadvatages
TACE	Target multiple tumours in one treatment session	No effect for hypovascular tumours, may induce liver or renalfailure
PEl	Minimally invasive	Limited to small lesions, need multiple treatment
PAl	Minimally invasive, probably more effective than PEl	Limited to small lesions, need multiple treatment
RFA	Effective for small and medium sized HCCs	Probably higher complication rate, more expensive
MCT	Effective for small and medium sized HCCs	Probably higher complication rate, more expensive
Combination therapy	Better response than single modality	Probably higher omplication rate due to additive risk

MCT, microwave coagulation therapy; PAl, percutaneous acetic acid injection; PEl, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolisation.

of HT was significantly lower than that for the best candidate for HR. In contrast a study by Figueras et al[37] showed that HT might provide better outcomes than HR (1-, 3-, 5-year DFS of 84%, 74% and 60% versus 83%, 72% and 51 %)

ADJUVANT TREATMENT AFTER HEPATECTOMY

Since majority of patients have microscopic residual disease at the time of liver resection there may be some role for adjuvant therapy; To date however, no study has demonstrated improved survival with adjuvant systemic chemotherapy[44,45] or immunotherapy.[46]

B. MANAGEMENT OF INOPERABLE HCC

For patients with unresectable disease the goal of palliative treatment is to control symptoms and prolong survival. Among the non-surgical interventions, transarterial chemoembolization, percutaneus ultrasound-guided therapy including injection of ethanol or acetic acid, and thermal ablation using radiofrequency or microwave energy; are the most commonly used methods (table 5). These loco-regional therapies possess the advantages of preserving the uninvolved liver parenchyma and avoid potential morbidity and mortality of major hepatic surgery.

A. TRANSARTERIAL CHEMOEMBOLIZATION (TACE)

TACE using iodized oil and chemotherapeutic agents combines the effect of targeted chemotherapy with that of ischaemic necrosis induced by arterial embolization. The HCC nodule usually has a high arterial blood supply. TACE can target single or multi-nodular HCCs in one treatment session and this could be repeatedly administered. A major limitation for treatment is the tumour size. TACE is ineffective for advanced stage (size > 5 or 6 cm) HCC. Histological studies of resected HCC specimens after TACE showed that complete necrosis occurred in only 22-50% of lesions and that TACE is particularly effective in treating tumours < 5 cm in diameter.[47] TACE results in increased risk of both hepatic and renal (because of the use of iodinated radio contrast medium) failure so that there is no significant improvement in the survival after TACE. The

risk of renal failure may increase when cumulative number of TACE sessions increase. Nonetheless a meta-analysis[48] has validated the efficacy of TACE as a palliative modality for inoperable HCC in appropriately selected patients. Another study[49] showed that TACE might be an effective alternative treatment in a subgroup of patients with potentially respectable HCC.

B. PERCUTANEOUS ETHANOL INJECTION (PEl)

The Japanese originally developed this in the 1980s when real-time ultrasound-guided aiming became possible. The injected chemical, pure ethanol induces local tumour necrosis as a result of direct protein denaturation, cellular dehydration and thrombosis of blood vessels. HCC is usually hypervascular and well encapsulated that can limit the spread of ethanol. Compared to the trans arterial approach, PEl is safer, less expensive and easy to perform. It also allows for selective treatment of HCC without significant damage to the adjacent liver parenchyma and hence can be used in moderately advanced cirrhosis. Side effects are minimal including abdominal pain, fever and transient impairment of liver function. Although the indication criteria for PEl differ among centers, nodules < 3 cm in size and = 3 in number are most suitable for PEI.[50] Small HCC< 3 cm treated by PEl may achieve a complete response rate of = 80%. The response rate drops significantly with increasing tumour size.[51] Non-randomized studies showed that patients undergoing PEI has a 3-year survival rate of 47-77%.[51] Tumour recurrence rate exceeds 50% in 2 years[52,53] probably due to metachronous or unnoticed synchronous tumours.[54] Comparison of PEl and surgical resection in small HCC in non-randomized series indicated that both groups might have a similar long-term survival.[55] Prospective trials are required to confirm this. PEl has been suggested as a rescue therapy for HCC patients not indicated for TACE or other non-surgical treatment.[56] Single sensation high dose injection of ethanol is a feasible alternative for unresectable HCC.[57]

C. PERCUTANEOUS ACETIC ACID INJECTION (PAI)

Acetic acid induces profound tumour necrosis at a concentration of 15-50% through a similar mechanism as ethanol.[58] The 5-year survival for small HCC (<3cm) using PAl is 49% .[59] Acetic acid has a strong ability to penetrate cancer cells, and can dissolve lipids and extract collagen from intratumoural septa and capsule that frequently contain viable cancer cells. Therefore it is superior to ethanol because the texture of the tumour and its resistance to perfusion with ethanol may make PEl less effective as also seen in a small randomized trial comparing PEl and PAl with the 2-year local recurrence rate being 44% and 10% respectively.[60] This study has shown poorer results with PEl compared to other studies. Another study showed similar results for PAl and PEl but demonstrated fewer treatment sessions and shorter hospitalization for the PAl group.[61] PAl can also be administered as a single high dose (upto 11 ml) session. There is no difference in the efficacy of treatment when compared to TACE with respect to progression-free survival or overall survival in case of tumours < 6cm or even in tumours < 3cm. However patients with tumour size of 3-6cm undergoing TACE had a better long-term survival than did patients who underwent PAl, suggesting that the effect of PAl for large HCC is still unsatisfactory.

D. RADIO FREQUENCY ABLATION (RFA)

Its use was first reported in 1993.[62] The puncture needle (or probe) has an insulated shaft and a non-insulated tip, which is inserted into the lesion under ultrasound or CT guidance. The patient is part of the electric circuit with grounding pads on the thighs or back. The radiofrequency energy emitted from the needle tip induces ionic agitation and frictional heat. The surrounding tissue, rather than the electrode itself, is the source of heat that destroys the cancer cells. RFA is an efficient local ablative therapy for HCC due to its excellent necrotizing effect. A randomized study showed the 2-year survival rate to be similar in patients undergoing RFA (98%) and PEl (88%) but patients undergoing RFA had a signiticantly lower recurrence (96% versus 62%).[63] The main reason for this is that the effect of PEl is highly

dependant on the diffusion pattern of the injected chemical within the tumour whereas the tumour necrosis zone in RFA is relatively fixed and predictable. Another advantage is that RFA can be used to treat medium or large HCCs upto 8 cm.[64] It still remains to be ascertained if RFA can serve as an alternate to surgical resection, especially in large HCC and well-compensated cirrhosis.[65] Recent data suggests that the complication rate may be higher with RFA than previously thought.[66] Also, when the tumour nodule is located close to the blood vessel, the radiofrequency energy will be carried away by the blood flow (the 'heat sink' phenomenon) and result in a sub optimal response. Needle-track seeding has been noted in 12.5% of patients 4-18 months after RFA in one study.[67] Post treatment tumour seeding is also a concern especially in case of subcapsular or aggressive tumours.

E. MICROWAVE COAGULATION THERAPY (MCT)

MCT utilizes a microwave coagulator that generates and transmits microwave energy to a needle electrode, which is inserted into the lesion. MCT can be applied with percutaneus or laproscopic approach to ablate unresectable HCC, and is useful to control tumour bleeding from ruptured HCC or prevent massive blood loss in liver surgery,[68,69] The response rate of MCT for small (< 3 cm) HCC was 70% but only 55% for large HCC.[70] The local recurrence rate was 2% for small and 8% for large HCC. The 3-year survival rate was between 73 and 86%.[71] In a study comparing MCT and PEl, MCT had better local control and longer survival for patients with moderately or poorly differentiated HCC.[72] Limitations and complications are similar to RFA including abscess or biloma formation, bleeding, liver failure and cancer dissemination.[73]

F. COMBINATION THERAPY

By combining different anti-tumour mechanisms (e.g. TACE and PEI,[74] TACE and MCT,[75] TACE and PAI,[76] RFA after arterial occlusion[77] treatment may be more effective. These approaches were efficacious for either small or large HCCs. Combination therapy frequently induces a higher rate of complete tumour necrosis and thus may reduce the incidence of intrahepatic metastasis significantly[78] but may also increase the risk of adverse events.

g. Other Methods: like percutaneus injection of hot saline or yttrium microspheres, interstitial laser photocogualation and cyroablation are seldom used now.[79]

RADIOTHERAPY

The use is limited due to low tolerance of the liver to whole organ radiation. In contrast to the relative ineffectiveness of whole liver irradiation when used alone, focal liver radiation can produce regression of some HCC[80,81] with either Yttrium[90] microspheres,[131] labeled ethiodized oil or external-beam radiotherapy (with either protons or photons).

CHEMOTHERAPY

Advanced HCC remains a challenge for medical oncologists. Almost all classes of chemotherapeutic agents have been tested in this disease yet none have shown substantial activity or a clear survival benefit. Thus, none can be realistically regarded as "standard of care". It is recommended that patients well enough to receive chemotherapy be encouraged to participate in a clinical trial. Doxorubicin is one of the most studied agents but has never been conclusively shown to have survival benefit compared with supportive care and the reported responses are extremely variable (Table 6). Studies have also not consistently demonstrated any combination to be superior to single-agent therapies. Of all the combination therapies, PIAF (cisplatin, interferon-alpha-2b, doxorubicin and 5-fluorouracil) has shown some promising results[82] that are being further evaluated in a randomized phase III trial. However this combination carries a high risk of morbidity and careful patient selection is required. HCC is resistant to standard therapies because of high mutational load it carries and the myriad of drug resistance mechanisms. This is in addition to the underlying liver dysfunction that imposes chemotherapy at even lower doses to mitigate toxicity. It is imperative that Child's-Pugh score be obtained before therapy and monitored thereafter. Patients With Child's-Pugh scores A or B can potentially receive treatment safely. Treatment should be stopped if their cirrhosis advances to Child's-Pugh C score.

Table 6: Response rates to chemotherapy in HCC

Drug	No. of patients	Objective response (%)
Capecitabine	37	13
Gemcitabine	20	5
Irinotecan	14	7
Paclitaxel	20	0
5-FU, Leucovorin	25	28
5-FU, Doxorubicin	38	13
Epirubicin, Etoposide	36	39
5-FU, IFN-μ	28	18
Cisplatin, IFN-μ	30	13
Cisplatin, 5-FU, Doxorubicin, IFN--μ	50	26

The available data suggests that chemotherapy is relatively ineffective in HCC. Hence, focus is on targeted therapy (figure l) like hepatocyte growth factor (over expressed in 33% of HCC),[83] Raf kinase inhibitors (BAY 43-9006)[84] and other investigational agents like erlotinib (OSI774) (epidermal growth factor inhibitor which is over expressed in about 17% of HCC)[83] flavopiridol (cyclin-dependant kinase 1, 2 and 4 inhibitor)[85] and antiangiogenic agents like thalidomide[86] and bevcizumab.[87]

IMMUNOTHERAPY

Although early diagnosis and treatment improve survival, HCC is rarely cured and recurs frequently after regional therapy or transplantation. Phase 2 studies have shown objective response rates of around 20%[88]. Takayama et al[89] postulated that immunotherapy would be most beneficial when used as a post surgical adjuvant since any residual tumour would be minimal. This group conducted a randomized trial using autologous lymphocytes activated vitro with recombinant interleukin-2 and antibody to CD3 post curative resection. The immunotherapy group had significantly longer recurrence-free survival (p=0.01) and disease-specific survival (p=0.04) than the control group although the overall survival did not differ significantly between groups (p=0.09).

SYSTEMIC HORMONAL THERAPY

HCC is more common in males. These tumours also express receptors for estrogens and androgens.[90] Tamoxifen not only inhibits the growth of HCC in vitro but also is a potential MDR reversing agent.[91] However large randomized studies have shown no survival advantage.[92,93] Antiandrogenic treatment with Ketoconazole and Cyproterone acetate has also been tried. Overall hormonal manipulation has a good theoretical basis, clinical data does not show any benefit.

RECURRENT LIVER CANCER

The prognosis for any patient with recurrent or relapsing disease is poor. The decision to treat and choice of treatment is influenced by prior treatment, site of recurrence, and presence of cirrhosis, hepatic function and patient preference. Re-resection should be considered whenever feasible.[94,95] Other options are transarterial oil embolization (TOC), PEl, chemotherapy or liver transplantation.[96] In one Hong Kong study,[96] out of 224 patients with intrahepatic recurrence following a curative resection, 105 developed recurrence. Eleven underwent re-resection with 1-,3-,5-year survival rates of 81 %, 60%, 69%; 71 patients received TOCE with 1-,3-,5-year survival rates

of 72%,38%,28%; 6 underwent PEl with 1-,3-5-year survival of 67%, 22%, 0%. Remaining 17 patients received systemic chemotheray or conservative treatment with no survivors at three years.

TREATMENT PLAN

This should be based on the extent of disease, growth pattern of tumour, hepatic functional reserve and the patient's performance status.

A. RESECTABLE TUMOURS

Standard treatment is partial hepatectomy or total hepatectomy liver transplantation

Neoadjuvant chemotherapy, chemoembolization or immunoembolization may make resection safer. Adjuvant chemotherapy or chemoembolization has shown no benefit in terms of overall survival or disease free survival.

B. UNRESECTABLE TUMOURS

No modality can be considered the standard of care. The choice and application of various loco-regional therapies vary from center to center and is likely to depend on the experience, preference and facility of that center.

PREVENTION OF HCC

The most effective means of preventing HBV related HCC is to prevent HBV infection by global vaccination of infants[97] WHO recommends the use of both a hepatitis B vaccine and human immunoglobulin (HBlg) (within 12 hours of birth) for effective control of perinatal transmission. The critical precondition for omitting HBlg is that the vaccine needs to be administered soon after birth. A routine antenatal screening program would be ideal but expensive and has been ruled out for all practical purposes. This makes it imperative that for the vaccine alone to protect a neonate; it should be delivered as soon as possible after birth and certainly within 24 hours. Dasgupta et aloo questioned the introduction of hepatitis B vaccine in the Universal Immunization Programme on the grounds of a) low coverage of immunizations at birth; b) wide variations in endemicity in India indicating basing the immunization policy on epidemiological need, state by state rather than nation-wide; c) short and long term financial sustainability. A study by Dhotilal et al[99] showed that patients with chronic liver disease of any etiology are at a higher risk for a more severe outcome when super infected with hepatitis A virus. Hence prevention of hepatitis B by inactivated vaccine has been shown to be safe and effective and is recommended in the west.

The incidence of HCC is slightly higher among hepatitis B e antigen positive persons suggesting that antiviral therapy that results in viral clearance or sustained suppression of HBV replication should reduce the incidence. Review of data[97] from over 1000 chronic hepatitis B patients who received interferon found that interferon has minimal overall effect on preventing HCC but a beneficial effect may be attained in responders. The negative results are due to small number of patients, short duration of follow-up and low response to interferon therapy in the only one prospective randomized controlled trial with Lamivudine using incidence of HCC as an endpoint. HCC was diagnosed in 3.9% patients in the study arm and in 7.4% in the placebo arm (p=0.047). Further studies are needed using anti-viral agents with lower risk of drug resistance to confirm these results. Meta-analyses of standard interferon monotherapy trials in patients with HCV-related cirrhosis suggest that interferon has a small but significant effect in reduction of HCC risk particularly in responders .[100]

There is an urgent need to establish a non-remunerated voluntary donor base in India. The use of sensitive laboratory test and the addition of core antigen (anti-Hbc) to the mandatory screening test list would further reduce the incidence of post-transfusion hepatitis.

Hepatocellular carcinoma meets most of the standard criteria for instituting a cost-effective surveillance program.[101] HCC surveillance aims to decrease disease-specific mortality, but this has not been demonstrated in prospective trials. One of the main problems has been the poor sensitivity and specificity of the available tools, AFP and ultrasound of the liver, for the early diagnosis of HCC. Prospective

studies evaluating the performance characteristics of AFP for HCC surveillance reported sensitivities of 39% to 64%, specificities of 76% to 91%, and positive predictive values of 9% to 32%.[102,103,104] A recent study evaluated whether surveillance in patients with cirrhosis improves survival.[105] The authors concluded that semiannual and annual surveillance equally improve survival of cirrhotic patients who go on to develop HCC by increasing the amenability to liver transplantation.

Tarao et al[106] showed that ursodeoxycholic acid (UDCA), which has anti-inflammatory properties in liver disease, significantly reduced the incidence of HCC (p=O.O36). Additional modifiable risk like excessive alcohol use, iron overload and diabetes/obesity need to be tackled. Retinoids[107] and Vitamin K2[108] might also prevent the development of HCC.

CONCLUSION

Surveillance of high-risk population is must for detection of liver cancer at early stages where curative therapy can be given. AFP is the most widely used tumour marker for HCC, but its diagnostic accuracy is poor. Proteonomic evaluation is an important tool in the discovery of novel proteins specific to hepatic carcinogenesis, which may lead to novel tumour markers as well as therapeutic targets. Liver transplantation remains the best therapeutic intervention that offers the longest disease-free interval. In selected patients with nonresectable HCC and good hepatic synthetic function, chemoembolization seem to offer a survival advantage versus no treatment. Otherwise, systemic chemotherapy has not been shown to be effective for the treatment of nonresectable HCC. Patients with HCC who cannot undergo curative procedures are best treated in the setting of a clinical trial.

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COMMENTS

I am delighted to be asked to comment on "Hepatocellular Carcinoma" by Parikh et al. They have covered all aspects of disease including incidence in India as well.

The clinical presentation of HCC differs depending on the coexisting liver disease. The patients may present with abdominal pain with a hepatic mass or with symptoms or signs due to liver cirrhosis. A proper screening programme of high-risk patient may help in early detection of cases as HCC may arise de novo in an otherwise normal liver or in patients with liver cirrhosis from regenerative nodules to dysplastic nodule and finally early to advanced HCC.

Imaging is performed for early diagnosis, correct staging and a follow-up of the treated lesion. Dynamic incremental CT / MR scanning of the liver during the non-equilibrium phase (dual and triple phase CT / MRI) and ultrasound with colour Doppler are the preferred methods for detection of HCC.[1-2]

The treatment of choice for HCC remains surgical resection or liver transplantation in carefully selected cases. However, the curative treatment (liver transplantation, surgical resection, percutaneous radiofrequency ablation) can only be carried out in <25% of cases. This is either because of operational contraindications (advanced cirrhosis in particular), the presence of locally advanced disease (multifocal lesions, invasion of the portal vein) or, more rarely, technical reasons (difficult to access sub-capsular/diaphragmatic locations).[5] Though the surgical resection of the tumour should be considered as the first choice of treatment it is mainly useful for small (<5 cm) peripherally situated tumours with good hepatic function giving a 5-year survival rate of 50%.[6] The causes of death in patients with HCC following surgical and non-surgical management show that the incidence of hepatic failure is high in post-operative patients. In order to increase the safety of major hepatectomy by preventing post-operative (right hepatectomy) hepatic failure, right portal vein embolization in non-cirrhotic liver is a very useful procedure. Following this procedure there is redistribution of portal blood flow with hypertrophy of remnant liver.[7] In patients not amenable to surgical intervention, variety of different percutaneous therapeutic interventional techniques have been investigated which have been very nicely covered in this review. TACE alone or along with PEI / PAI has shown better tumour response rate than systemic chemotherapy. The commonly used chemotherapeutic agents in TACE are epirubicin, mitomycin-c and cisplatin. We have compared TACE alone and TACE combined with PEI in some large encapsulated lesions and found the combination to be better. I want to add one more option (radionuclide therapy) in this list of interventional therapies for the treatment of unresectable HCC. Studies using radionuclides such as iodine-131, yttrium-90 microspheres, holmium-166, phosphorus-32 and rhenium-186 conjugated to monoclonal antibodies, lipiodol or chemical compounds and injected systemically or transarterially have shown good but variable results. The aim of internal radionuclide