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MANAGEMENT OPTIONS FOR PRIMARY HEPATOCELLULAR CARCINOMA

An overview

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Hepatocellular carcinoma (HCC) is the seventh most common cancer in men and the ninth most common cancer in women with 500 000 to 1 000 000 new cases per year. Several risk factors (sex hormones, alcohol, thorotrast, aflatoxin B_1, hepatitis B or C, haemochromatosis, α_1-antitrypsin deficiency, tyrosinemia, porphyria cutanea tarda, acute intermittent porphyria, Wilson's disease) associated with the development of HCC have been identified from epidemiological studies. The diagnosis is usually based on a combination of clinical and laboratory findings together with radiographic and histopathologic characteristics. HCC remains difficult to treat with a median survival of 3 to 6 months after the onset of symptoms. Surgical resection is the mainstay of treatment for HCC. Transcatheter arterial embolization and percutaneous ethanol injection have been used but neither therapy has been evaluated in a prospective randomized study. Combination treatment (e.g. chemotherapy and resection) may be of value but randomized controlled trials with long-term follow-up are still needed. Liver transplantation should be reserved for carefully selected patients.

Hepatocellular carcinoma (HCC) is a frequent clinical problem, especially in the management of patients with chronic liver disease. It is more common in men with a sex ratio of 3:1 and its maximal incidence rate occurs in the 5th and 6th decades of life (1, 2).

Extensive epidemiological studies have revealed a clear association between chronic hepatitis B and C virus (HBV and HCV) infection and HCC (3). It is believed that 80–90% of patients with HCC have HBV-induced liver cirrhosis. In a recent study of 917 patients with chronic hepatitis or compensated liver cirrhosis, Cox's regression analysis showed that the risk of liver cancer was increased almost seven-fold in patients with hepatitis B surface antigen and four-fold in patients with hepatitis C antibody (4). Molecular studies have indicated potential mechanisms which might account for a direct role of HBV in liver carcinogenesis: integrated HBV DNA sequences are present in tumour cells and may lead to mitogenesis (5). On the other hand, the viral protein X could act as an activating factor on cellular genes (5). Cirrhosis from almost any cause (alcoholism, haemochromatosis, α_1-antitrypsin deficiency, primary biliary cirrhosis) is associated with an increased risk of HCC (3). Widespread infection with clonorchis sinensis is at least partly responsible for the higher incidence of HCC in Asia whereas aflatoxins (fungus metabolites), found in staple food in Africa, are also contributing to HCC pathogenesis (3).

The prognosis depends on the stage of the tumour and the degree of liver function impairment. The simplest clinical staging system is that proposed by Okuda et al. (6) based on the presence or absence of ascites, tumour > 50% of the two-dimensional size of the liver, serum albumin < 30 g/l and serum bilirubin > 30 mg/l. It is therefore obvious that screening programmes aiming at discovering small HCCs in populations at risk (patients with chronic liver disease) are mandatory.

Management

Various treatment modalities have been proposed for patients with HCC. Surgery is generally considered as the

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only option for significant long-term survival. However, for patients who cannot undergo resection, either because of severe cirrhosis, age, multifocality, site of the lesion, or refusal of surgery, there are several palliative options available.

Percutaneous ethanol injection (PEI) under the guidance of ultrasound has given promising results. Alcohol causes cellular dehydration with protein denaturation of tumour cells, the consistency of which is softer than the surrounding cirrhotic tissue, thus allowing an easier and elective perfusion of the neoplastic tissue, leading finally to coagulation necrosis (7). It has been shown that PEI is a safe, inexpensive and appropriate treatment for cirrhotic patients with small HCCs (< 3 cm) and inoperable lesions (< 5 cm), where the one-, two-, and three-year survival rates were 96%, 90% and 75% respectively (8). However, PEI is a loco-regional treatment option and consequently it is appropriate only when the tumour is single and small (8).

Cryosurgery with liquid nitrogen and a probe temperature of 180°C has also been evaluated in patients with unresectable HCC. In a series of 70 patients with HCC treated with cryosurgery the one-, two-, three-, and five-year survival rates were 59.1%, 37.5%, 27.0%, and 12.5% respectively (9). Cryosurgery has the advantage of destroying the tumour in situ with minimal damage of the surrounding normal liver parenchyma, or large blood vessels; it has also been suggested that it results in increased immunological stimulation, possibly by sensitizing the patient-to-tumour antigens (10). However, despite its therapeutic potentials, hepatic cryosurgery has its limitations: bile duct damage could lead to late stricture formation, repeated freezing of separate areas significantly prolongs operation time and finally, the optimal tumour size should be smaller than 7 to 8 cm in diameter (11).

Surgery, whenever possible, remains the best treatment, although it is associated with a high incidence of intrahepatic recurrence (12). Developments in surgical techniques, better pre- and postoperative management, and improved preoperative evaluation of hepatic functional reserve to prevent postoperative liver failure, have lowered the operative mortality rate to less than 10% in most series (12). It is estimated that 90% of tumours are unresectable at presentation because of tumour size, location or underlying paraenchymal disease, and recurrence after resection accounts for nearly 50–90% of postoperative deaths (6). The role and the objective of surgery in the treatment of HCC are curative resection in the early stage and prolonged survival with improved quality of life by palliative procedures in the advanced stage. In a recent study conducted by the Liver Cancer Study Group of Japan involving 30 000 patients from 601 hospitals over a 27-year period, the survival rates of patients with curative resection were 77.4% at 1 year, 64.8% at 2 years, 55% at 3 years, and 36.6% at 5 years, whereas those of the non-curative group were 66.6%, 47.8%, 34.7% and 23.3% respectively (13). The difference between the curative and non-curative surgery groups was statistically significant (13). The American experience of Pittsburgh over a 23-year period was similar. The 1-, 3-, and 5-year survival rates of patients with primary hepatic malignancy following curative resection were 68.5%, 45.1%, and 31.9% respectively (14). Although many European groups are now reporting their early experience of resection for HCC in cirrhosis, preliminary data suggest that the results are almost similar to those reported in southeast countries. An analysis of the results of nine European studies, involving a total of 222 patients with HCC (half of which had alcoholic cirrhosis), revealed a 2-, 3-, and 5-year survival rate of 64%, 58%, and 45% respectively (15). As outlined in Table 1, similar results have been also reported by recent series with a 1-year survival rate between 66% and 100%, and a 5-year survival rate between 25% and 39.5% respectively (16–21). Hepatic artery ligation is of no proved value in terms of prolongation of survival in patients with unresectable HCC. The effect of interruption of the arterial inflow is of short duration because of the rapid development of arterial collaterals with a reported mean survival time averaging 17 to 21 weeks (22). Although the high incidence of recurrence following curative resection can be attributed in part to the associated liver cirrhosis (23), tumour size (> 5 cm), tumours with daughter or multiple nodules, portal vein involvement and HCC with pattern III ploidy (aneuploid with ± 2 G0/G1 peaks) constitute absolute risk factors for tumour recurrence (24). It is therefore believed that measuring DNA ploidy may provide a new treatment strategy for HCC after curative resection (24). Furthermore, a recent study showed that absence of antibody to hepatitis C virus was also significantly associated with recurrence after curative resection, whilst the size of the tumour did not affect the incidence of recurrence (25). In the same study, cumulative recurrence rates of 37.0%, 57.1%, and 71.6% at the end of the 1st, 2nd and 3rd year following curative resection were reported (25). Early recognition of tumour recurrence after curative resection of HCC is paramount importance; aggressive multitherapy regimens, rather than surgery only, are essential to prolong the survival time.

Table 1

Resection for hepatocellular carcinoma

Ref	No. of patients	Perioperative mortality (%)	Survival (%)		
			1 yr	3 yr	5 yr
(16)	94	8	76	41	—
(17)	67	8	76	49	25
(18)	119	9	80	47	39
(19)	76	—	71.1	47.2	32.9
(20)	118	—	100	71.1	39.5
(21)	33	3	66	37	—

Table 2

Liver transplantation for hepatocellular carcinoma

Ref	No. of patients	Perioperative mortality (%)	Survival (%)		
			1 yr	3 yr	5 yr
(28)	87	13	55	30	20
(29)	80	13	64	45	45
(30)	44	16	63	34	30
(31)	29	0	61	46	—
(32)	27	11	82	71	—

Liver transplantation for HCC arising in cirrhosis aims at curative tumour removal in cases where partial hepatic resection is not possible because of the extent of tumour inside the liver, and/or significantly impaired liver function. Compared to conventional liver resection, transplantation has the theoretical advantage that the risk of tumour recurrence due to undetected small liver tumour foci or to 'de novo' HCC nodules arising in the remaining cirrhotic parenchyma, is reduced (26). Significant data can be obtained from the experience at Hannover and Cambridge. At one year, the survival rate was 48.3% in Cambridge and approximately 35% in Hannover and at two years 38.3% and approximately 30% respectively (27, 28). The results of liver transplantation for the treatment of HCC are outlined in Table 2 (28–32). The ranges of the 1- and 5-year survival rates were 55% to 82% and 20% to 45% respectively. However, recurrence rates as high as 65% have been reported (27). Iwatsuki et al. (19) compared the results obtained by liver transplantation ($n = 105$) to those achieved by hepatic resection ($n = 76$) over a 10-year period. Overall 1- to 5-year survival rates of the resection group were 71.1%, 55.0%, 47.2%, 37.2%, and 32.9% respectively, and those of the transplantation group 65.7%, 49.0%, 39.2%, 35.6%, and 35.6% respectively; the overall tumour recurrence rate was also similar for the resection and transplantation groups (50% vs 43% respectively; $p > 0.05$) (19). In a recent study, survival and recurrence rates after hepatic resection or transplantation for HCC in cirrhotic patients were analysed (33). In terms of survival rates, resection and transplantation yield the same results (50% vs 47% respectively, at 3 years). For transplantation, however, the rate for survival without recurrence was better than that for resection (46% vs 27% respectively; $p < 0.05$). In the case of the small uninodular or binodular tumours (< 3 cm), transplantation had much better results than resection (survival without recurrence, 83% vs 18% respectively; $p < 0.001$) (33). It is therefore believed that the best indication for transplantation seems to be patients with small and uninodular or binodular tumours (< 3 cm) (33). However, in the light of lack of donor organs and of the relatively overall unfavourable results of liver transplantation in cirrhotic patients with HCC, controversy regarding indications still remains.

Medical treatment of HCC not amenable to resection has so far given disappointing results. Systemic chemotherapy, either as single agent or polychemotherapy regimens, resulted in equivocal or inapplicable conclusions (34). Doxorubicin (adriamycin) has been extensively studied; it has certain advantages, e.g. high liver concentration after intravenous administration and low renal/hepatic toxicity which is independent of cell division, and applies to cells with low mitotic activity, such as hepatocytes (35). The response rate after intravenous administration of doxorubicin at a dose of 70 mg/m^2 for 3 weeks is at most 20%, and even less in cirrhotic patients (35, 36). Falkson et al. (37) reported the experience of the Eastern Cooperative Oncology Group with intravenous chemotherapy for HCC in 432 patients who were treated on four consecutive randomized chemotherapeutic protocols including combinations of 5-fluorouracil (5-FU), streptozotocin, semustine, doxorubicin, zinostatin, amsacrine, and cisplatin. The median survival for all patients was 14 weeks with only 14% surviving more than 1 year. A median survival of 6 weeks was observed with oral 5-FU and of 24 weeks with a combination of intravenous 5-FU and semustine (37). It was also found that doxorubicin alone or in combination was more effective than oral 5-FU (37). Similar results have been published by Ihde et al. (38).

The results of ongoing studies involving hormonetherapy and on target treatment are awaited; initial results with hormonetherapy were negative, but although reduction in tumour size is not observed, long-term inhibition of sexual steroids may lead to a decreased rate of tumour cells turnover in patients with tumour receptors to those hormones (progestogens, anti-oestrogens, anti-androgens, LH-RH agonists) (39, 40). Recently it has been shown that injection of chemotherapeutic agents or radionuclides mixed with lipiodol ultrafluid (an oily contrast medium enhancing the tumour response) into the hepatic artery seems to give encouraging results in terms of tumour response and, possibly, of survival (41). The number of reported cases is, however, limited and the response rate remains still low (42, 43). With this kind of treatment side-effects are reduced, provided the patients have good hepatic function without any portal vein thrombosis. The value of antibodies or radionuclides for targeting chemotherapy remains to be determined, although initial reports show reduction in tumour size with a similar decrease in serum α-fetoprotein levels (44, 45). Experience with immunostimulant or immunomodulatory drugs for the treatment of HCC is still limited. Interferons (IFN) possess antiproliferative and immunomodulating properties suggestive of a possible antitumour effect. IFN-α and IFN-γ have been tested either alone or in combination with doxorubicin in patients with HCC; even at high doses, the results were disappointing in terms of response, survival, and side-effects (46–48). Lymphokine-activated killer cells (LAK) have cytolytic activity against a wide

variety of tumour cells (49); they could be generated in vitro by incubating mononuclear cells from peripheral blood with interleukin-2 (49). Initial experience on the use of LAK cells in HCC suggests that they are effective in combination with interleukin-2 when delivered via the hepatic artery, interleukin-2 alone being inactive (50). However, further evaluation is required to elucidate the exact role of this promising treatment option.

Combination surgery and multimodality treatment should be considered for patients with unresectable HCC. Initial studies showed that 11 patients with HCC, judged unresectable at laparotomy, subsequently underwent resection after significant partial remission induced by either radiolabelled antibody treatment, or external beam radiation in combination with chemotherapy (51). Recently, 14 patients with unresectable HCC underwent combined external beam radiation with 21 Gy, and 15 mg doxorubicin with 500 mg 5-fluorouracil, radiolabelled polyclonal antiferritin immunoglobin conjugated with ^{131}I in 9 patients and with 90 yttrium in one case (52). Tumour reduction greater than 50% was noted in all patients, and resection was then performed with a 5-year survival of 48% (52). It is, therefore, believed that in some patients unresectable HCC may successfully be converted into resectable with a combination of irradiation and chemotherapy. Similar good results have also been obtained with percutaneous trans-catheter hepatic arterial chemotherapy and embolization for unresectable HCCs which subsequently were successfully excised (53). A combination of cisplatin, mitomycin C, 5-fluorouracil and ethiodized oil (Lipiodol) or absorbable gelatin sponge was given in 30 patients with large HCC; tumour diameter was reduced by $31.6 \pm 15.2\%$ and the present tumour necrosis ranged from 40 to 100% (53). All patients underwent liver resection with survival rates of 88.89%, 77.03%, and 77.03% at the end of the 1st, 2nd and 3rd year respectively (53). This multimodality treatment, therefore, appears promising for patients with advanced primary liver malignancy but further evaluation and assessment are required.

Conclusions

Hepatocellular carcinoma is responsible for at least one million deaths a year worldwide, constituting about 80% of primary liver tumours (54). In approximately 70% of patients, the tumour has already spread outside the liver when HCC is first diagnosed, resulting in a dismal prognosis with a median survival time of less than 6 months in untreated patients (2).

Although curative resection is the optimal treatment, it is feasible in only 25% of patients and is associated with a high incidence (up to 75%) of intrahepatic recurrence (2). An operative mortality of 3 to 9% is now generally reported (Table 1); however, whenever cirrhosis is present the mortality rises to as high as 25% (55). Promising predictors of operative mortality focus on the mitochondrial function of hepatocytes and include cytochrome a ($+\alpha_3$) contents and the redox tolerance index (56). The 5-year survival rate for patients after curative resection of HCC without cirrhosis is about 40% (20); on the contrary, the survival figures after liver resection for HCC in patients with cirrhosis range from 55 to 85% at 1 year, from 26 to 58% at 3 years, and decrease to less than 15% at 5 years (56). Survival after resection is affected by two factors; the underlying liver disease and recurrence of the tumour. Poor liver function is predictive of late mortality and more than half of the patients in Child's group B and C die of progression of their liver disease within one year without any tumour recurrence (57). On the other hand, intrahepatic metastasis, portal vein tumour thrombosis and satellite nodules have been demonstrated to be the major predictors of recurrence following curative resection for HCC (58). In a recent study of 252 patients who underwent complete resection for HCC, the effect of perioperative blood transfusion on the recurrence of carcinoma was evaluated (59). Carcinoma recurred in 55 (74.3%) of the 74 patients who received a transfusion, but in only 89 (50%) of the 178 patients who did not receive a transfusion ($p = 0.0001$), this effect being significant even when only a small amount of blood was transfused ($p = 0.0001$) (59). It is suggested that the recurrence of HCC by perioperative blood transfusion may be caused by suppression of an antitumour immune mechanism (59).

Hepatic resection should be used in patients with unifocal tumours, multifocal tumours confined to one lobe, and normal or mild-to-moderate dysfunction (Child's class A or B) (21). Unresectable tumours should be treated initially with either transarterial embolization alone or in combination with percutaneous ethanol injection followed by resection should considerable tumour shrinkage occur. Peritoneal seedlings, cancer cachexia or disseminated carcinomatosis are considered absolute contraindications for hepatic resection (60).

The results of liver transplantation have been disappointing in patients with unresectable tumours (30). In cirrhotic patients with resectable tumours, liver transplantation should be considered; however, the dilemma faced by the clinician in choosing between resection and liver transplantation is difficult to resolve. Careful patient selection (such as centrally located tumours, tumours unresectable by conventional techniques but confined to the liver, multifocal tumours in more than one lobe, Child's class B or C function with small HCC), remains crucial because of the limited resource of donor's livers (32).

Recurrent tumours (and primary advanced tumours that cannot be resected) may be treated by one of the available palliative options, such as transcatheter arterial embolization, targeted chemotherapy, percutaneous alcohol injection, and cryosurgery in association or not with resection (61). Recent data showed that treatment of HCC with

transcatheter arterial embolization is well indicated regardless of tumour size for patients with non-advanced liver cirrhosis and uninodular tumours (62). The cumulative survival after transcatheter arterial embolization in 87 patients was significantly longer ($p < 0.0001$) in patients with uninodular tumours than in patients with multinodular tumours (3-year survival 53.3% vs 13.3%; 5-year survival 32.2% vs 3.3% respectively) (62). In contrast, patients' survival time was not associated with the size of the tumour detected at the time of treatment ($p > 0.1$) (62). Initial experience also showed that liver cryosurgery is an effective treatment in selected patients (tumour adjacent to major blood vessels is likely to persist because of inadequate freezing) (63). Further investigation, however, into cryosurgery (and also immunotherapy) is needed before their clinical use can be recommended.

In conclusion, early diagnosis offers the best chance to cure, and careful monitoring of patients with chronic liver disease, particularly cirrhosis, has made it possible to detect HCCs at an early stage. Although measurements of the alpha-fetoprotein L_3 and alpha-fetoprotein allow the differentiation of HCC from cirrhosis and serve as predictive markers for the development of HCC during the follow-up of patients with cirrhosis, a randomized trial comparing total alpha-fetoprotein with fractionated alpha-fetoprotein levels at the time of diagnosis of HCC has yet to be done (64). Elective liver resection still remains a major operation but has become a safe routine surgical procedure. We strongly believe that patients with unresectable HCCs should be included in randomized controlled trials to assess and quantify the remote possibility of any 'surgical advantage', possibly associated with combination treatment.

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