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Treatment of primary liver cancer in Singapore A review of 3200 cases seen between January 1, 1977, and July 31, 1987

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Summary. Between January 1977 and July 1987, 3200 patients with hepatocellular carcinoma (HCC) were studied in Singapore. HCC formed 90% of primary liver cancers seen in Singapore and is the second most common fatal malignancy seen in men in the country. Extensive clinical and basic research has defined certain treatment strategies. Of importance is the prompt detection of early nodular tumours, which can be resected. Resection, 'targetting' with anticancer drugs and, in selected cases, synchronised direct hepatic irradiation with adriamycin, used as a radiosensitiser, have been promising treatment methods. Biological modifiers, such as interferons and interleukins, offer potential for the future. Preliminary pilot studies suggest that interferons may prevent the development of HCC, but more studies are required. Similarly, selective localisation of anticancer agents with radio-isotopical agents opens opportunities for treatment.

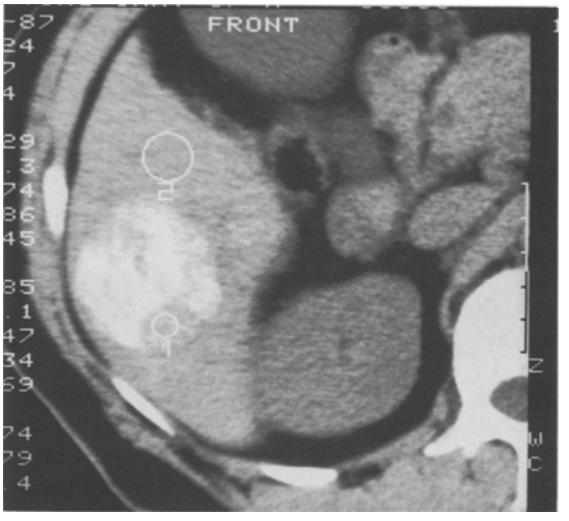

Fig. 1. Small hepatocellular carcinoma of 5 cm diameter detected on screening in a 57-year-old Chinese male patient, HBsAg-positive, anti-HBs-positive. Computerised axial tomography done two weeks after hepatic arterial injection of lipiodol, showing retention of contrast in the tumour nodule

Epidemiological factors

Primary hepatocellular carcinoma (HCC) is the foremost primary liver cancer in Singapore and accounts for up to 90% of primary liver cancers, the rest being due to carcinomata of indeterminate origin, and angiosarcomas. It occurs in all three ethnic groups, Chinese, Malays and Indians, and is the third most common cancer amongst men with a crude rate of 19.8 per 100000 and an age-standardised rate of 28.1 per 100000 [1]. In 1984, liver cancer was the second most common fatal cancer in male Singaporeans, ahead of cancers of the stomach and colon, and second only to lung cancer [6].

Ethnically, primary liver cancer was the second most common fatal cancer in Malays, and the third commonest in Chinese and Indians (Table 1).

Clinical features

HCC continues to present late in the majority of patients. Only when regular ultrasonographic screening, combined with α-foetoprotein and γ-glutamyl transpeptidase analysis were introduced last year, have smaller tumours of less than 5 cm been identified. Nevertheless, most patients present with abdominal discomfort, pain or various other manifestations (see Table 2).

Radiologically there are three patterns (Figs. 1-3) identified on hepatic angiography: (a) single and nodular; (b) multicentric and (c) diffuse infiltrating lesions.

Single nodular lesions are uncommon and comprise 2% of our HCC. In most instances, with few exceptions, they are positive for α-foetoprotein and γ-glutamyl transpeptidase and can be detected by ultrasonography. These groups have the best prognosis since resection and 'targetted treatment' are possible. However, the majority of these lesions present as masses over 5 cm in diameter, more often in the right lobe than in the left. In 40 resected cases, followed for up to 1 year and untreated with chemotherapy thereafter, the recurrence rate was 50%. When these relapses developed, the rest of the liver was also diffusely involved (Table 3).

Both the multicentric and diffuse infiltrating lesions have a bad prognosis with median survivals of less than three months, and fewer than 5% survive 1 year untreated. Our longest untreated survivor with nodular HCC lived for 3.5 years. Where jaundice was detectable at

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Table 1. Changing trends in cancer incidence in Singapore

Cancer incidence in Singapore

Period		1	2	3	4
1968–1972		Lung	Stomach	Liver	Colorectal
1973–1977		Lung	Stomach	Liver	Colorectal
1978–1982		Lung	Stomach	Liver	Colorectal
Male and female cancer mortality for the top three most frequent cancers					
Year	Sex	1	2	3	
1982	M	Lung	Stomach	Liver	
	F	Breast	Colorectal	Lung	
1984	M	Lung	Liver	Stomach	
	F	Lung	Colorectal	Breast	
Sex	Ethnic group	1	2	3	
M	Chinese	Lung	Stomach	Liver	
	Malays	Lung	Liver	Colorectal	
	Indians	Stomach	Lung	Liver	
	Chinese	Colorectal	Breast	Lung	
	Malays	Breast	Cervix	Ovary	
	Indians	Breast	Cervix	Colorectal	

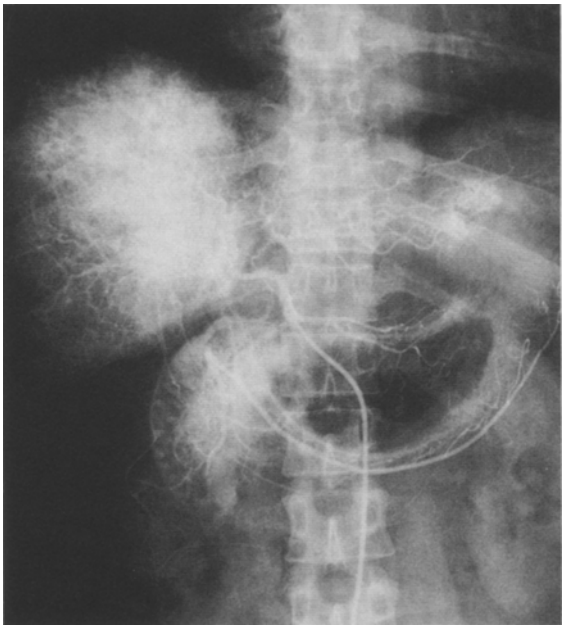

Fig. 2. Diffused infiltrating primary hepatocellular carcinoma in male Chinese patient aged 40 years, HBsAg-positive, α-foetoprotein 600000 ng/ml. Refractory to chemotherapy; succumbed 8 weeks after onset

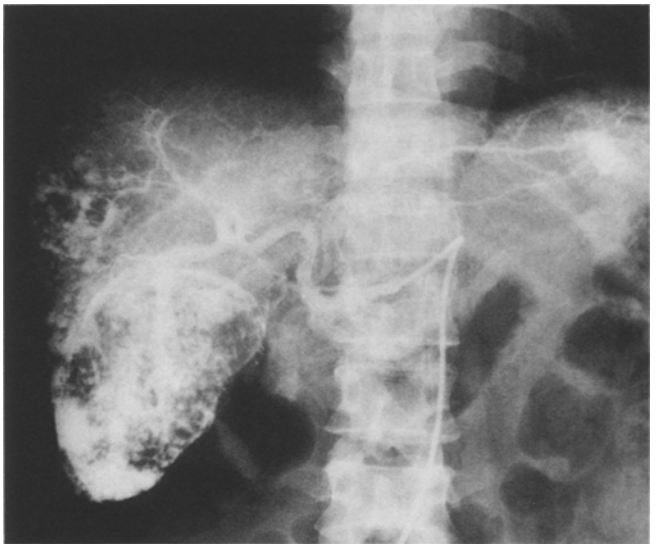

Fig. 3. Multi-nodular hepatocellular carcinoma in female Malay patient aged 38 years. Responded to hepatic arterial injection of lipiodol and adriamycin. Partial remission for 10 months

presentation, the median survival time was less than 3 months; in such cases, progression to ascites, ankle oedema, hepatic encephalopathy, haematemesis and malaena or pulmonary metastases was rapid. Where pulmonary metastases occurred, ECHO cardiography has shown intracardiac metastases.

Treatment

At present the two most effective regimes are (a) surgical resection and (b) targetting of the anticancer agents adriamycin and mitomycin, following lipiodol given by selective hepatic arterial cannulation and subsequent embolisation with Gelfoam. These have led to rapid tumour necrosis with signs of tissue infarction, such as pain and fever.

Both of these treatments are effective against nodular HCCs. In the multicentric HCC, targetting of these drugs has produced pronounced tumour regressions where both tumour masses and α-foetoprotein levels have fallen by more than 50% two weeks after the procedure. However, these regressions are temporary and cannot be sustained indefinitely. The longest survivor by this method in 20 cases was 1 year.

Table 2. Clinical features of primary hepatocellular carcinoma in Singapore[a]

Clinical feature	Frequency (%)
Abdominal discomfort	90
Liver mass	95
IVC obstruction	50
Abdominal pain	80
Dysphagia	50
Ascites	50
Septicaemia or fever or abscess	40
Mucoid diarrhoe	40
Haematemesis and malaena	40
Pulmonary metastases	20
Cardiac metastases	20
Renal failure	40
Skeletal metastases	10
Neurological metastases	3
Lymph node metastases (cervical)	1
Rupture	5
Hypoglycaemia	10
Intestinal obstruction	5
Encephalopathy	20
'Collapsing pulse'	95
Bruit over liver	60
Hepatic rub	60
Associated polycystic liver	1 case
Associated Wilson's disease	1 case
Associated with haemophilia	1 case
Associated polycythaemia	5
Associated thrombocystosis	5
Pancreatic involvement	3 cases
Occurring in two boys (HBsAg pos.) aged 8 years	

[a] 3200 cases were seen between January 1, 1977, and July 31, 1987

Table 3. Radiological patterns and survival time

Pattern	Frequency (% of cases)	Prognosis	Median survival (months)	Longest survival (months)
Nodular	(2)	Good	6	36
Multifocal (multicentric)	(18)	Poor	3	12
Diffuse infiltrating	80	Bad	3	6

Since March 1985, this method of treatment has been introduced for all our inoperable HCCs and other HCCs that have relapsed following surgery. Of the 40 treated by this method, there are 8 (20%) patients in complete remission, who are tumour-free and alive after 2.5 years of follow-up. These patients belong to the small group with nodular HCC less than 5 cm in size when the recurrences took place, or with a tumour inoperable because of location, and about 10 cm in diameter.

Multicentric lesions have also responded to this treatment, but the diffusely infiltrating form is highly malignant and though α-foetoprotein levels may fall significantly by 90%, rapid recurrences occur within a month, indicating the presence of highly resistant clones of tumour. Early this year, Aw and Sundram in our laboratories tagged lipiodol to ^{131}I (30 mCi) and we treated ten patients with this in combination with adriamycin (20 mg) given by direct hepatic arterial injection. Scanning of the liver and urine showed retention of ^{131}I in the liver for 48 h but there was high excretion in the urine after 48 h. No regressions of tumour were seen in the ten treated patients during the 4–8 week follow-up. This may suggest that ^{131}I may not be a suitable material for tagging to lipiodol because of its rapid loss, but the selective localisation in tumour cells of a cytotoxic drug with a radioactive material may be a better method of destroying tumour cells in rapid mitosis or in the resting state. Further developments in this area are required since a direct method of delivery of anticancer agents combined with the local retention of the drugs is now possible.

Other modes of therapy

Intravenous administration of anticancer agents has been disappointing, even when active agents such as adriamycin, mitomycin and epirubicin have been used at optimum dosage. For instance, in the 10-year follow-up of our first clinical trial in 1978 [5], using a combination of prednisolone, adriamycin, vincristine and 5-fluorouracil, we found this combination to be slightly more effective in the first 2 months than adriamycin alone, but after 1 year the survival was the same for adriamycin alone or in combination. There was 17% survival with each type of treatment compared to nil in the untreated controls. Out of all the 34 patients treated by chemotherapy in this study, only 1 (3%) survived for 10 years and is in remission. This patient had a 10-cm nodular HCC localised between the right and left hepatic lobes, which therefore was not resectable.

Anticancer agents

We have also explored other agents [3] but found all to be ineffective: carbimazole, cyclophosphamide, 5-fluorouracil alone, methotrexate, thiotepa, futraful, methyl-CCNU, bleomycin, cisplatin, VP 16-213, and intrahepatic arterial injection of neocarzinostatin. However, more recently we have found that carboplatin is well tolerated and has significant activity in pilot studies. These studies are still in progress.

Hormonal manipulation

In 1980 [4], we also explored the possibility of testosterone deprivation in advanced HCC, following experimental evidence that androgenic hormones could easily induce HCC in animals pretreated with aminobenzene. Subsequently, in human HCC cell-culture studies, we were able to identify the presence of both oestrogen and testosterone cytoplasmic receptors [7]. These were also confirmed by Friedman (personal communication). Elevated levels of free L-thyroxine in the serum have also been found in many of our HCC cases and, in murine hepatomas, HCC have been slowed by thyroidectomy, radioactive iodine or propylthiouracil. Glucagon and insulin receptors have also been detected in murine HCC and correlated with tumour growth rates. Insulin, glucagon and hydrocortisone are known hepatotrophic factors to normal liver tissues. In a survey of 20 advanced human HCC conducted under basal conditions, we have found raised growth hormone (prolactin) levels in 90% of the cases but radio-immunoassayable insulin levels were below normal. Growth hormone levels were normal in patients in clinical remission.

In 1980, six patients with advanced HCC, bilateral orchidectomy was performed to remove testosterone dependence, which was also confirmed by an inability to detect their serum testosterone. However, in close follow-up, there was no correlation between negative testosterone levels and the rapid growth rates of these tumours. Androgenic deprivation, therefore, did not influence the growth rates of these tumours, and the use of aminoglutemide in 20 unselected patients, to produce androgen, proges terone and hydrocortisone deprivation, did not alter the growth rate of these tumours when tested in our advanced HCC.

These studies indicate that there is a limited role for hormone manipulation for advanced HCC.

Synchronised hepatic irradiation and adriamycin

In 1978, a clinical study was conducted on advanced inoperable HCC using a split dosage of hepatic irradiation (150 rad per day to a total dose of 3150 rad). This was given synchronously with 10 mg adriamycin three times a week for three weeks. Of the 30 patients entered into the study, 50% survived for 6 months compared to 3 months in the controls. Patients with large lobulated HCC, localised to one region, who had no jaundice, ascites or renal failure, were the ones who responded to the treatment. It was not suitable for patients with jaundice, ascites or renal failure. Of the 30 patients, 3 (10%) survived for 5 years and are in partial remission.

Immuno-modulators (biological modifiers)

The recent availability of α and β interferons has led us to explore the use of lymphoblastoid interferon in two sets of circumstances: first, for advanced HCC, when used in conjunction with the present targetted treatment of adriamycin, mitomycin and lipiodol and, secondly, as immunoprophylaxis following complete remission of HCC. These patients were also treated for their chronic hapatitis B virus (HBV) infection synchronously, and levels of HBV DNA, HBsAg and anti-HBe were monitored.

In the first group, between 30 MU and 60 MU lymphoblastoid interferon were given to six patients with advanced HCC, together with perhepatic arterial injection of adriamycin and mitomycin. No significant regressions were seen and tumour masses remained the same size; nor was there any fall in the levels of α-foetoprotein.

In the second group, six patients, who were treated with 3-monthly cycles of 30 MU lymphoblastoid interferon followed by ketoconazole (known to suppress HBV DNA in in vitro studies on human HCC), remained tumour-free after 2.5 years. In contrast, two untreated control cases, who were untreated by interferon and ketoconazole, have relapsed after 1.5 years.

The basis for our using lymphoblastoid interferon is also that HBV DNA is demonstrable in the circulating leucocytes in all our HCC cases [2] even though 20% of our HCC cases are HBsAg-negative. Thus, the recruitment of natural killer cells and the restoration of deficient interferon levels and impaired immunity may be important host immune regulatory factors against both HCC and HBV.

Prospects for the future

In established HCC cases, selective targetting of active anticancer drugs, prolonged retention of these drugs locally in the tumour and their subsequent ability to eliminate malignant clones have been shown in a few cases. The present difficulty is to consolidate such regressions that have occurred or to eradicate repeating appearances of malignant clones. The use of lipiodol tagged to an anticancer agent and radioactive material is, therefore, an important tool to be developed for future therapy.

In the longer term, early treatment of all chronic hepatitis B cases with suitable antiviral drugs is needed. Between October 1986 and September 1987, no HCC developed in 300 chronic HBV cases treated regularly with lymphoblastoid interferon, after 1 year of close follow-up at six-weekly intervals. On the other hand, 5 out of 50 untreated patients in an age-matched group of 50 years developed HCC within 4 months after their last screening. A review of the literature of antiviral therapy for chronic HBV infections, has shown no reported HCC cases in those treated with antiviral agents since 1980. It is possible, therefore, that antiviral therapy and immunomodulators may play some role in the prevention of HCC by reducing further inflammatory hepatic damage and further HBV integration. More studies are required to determine the role of these biological modifiers and their mechanism(s) of action.

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