

Surgical treatment of hepatocellular carcinoma

by Dr Edward C S Lai

Hepatocellular carcinoma (HCC) is prevalent in areas with a predominantly Chinese population, such as China, Taiwan and Hong Kong.

According to government statistics, HCC has been the second leading cause of cancer-death in Hong Kong for the past twenty years.

Advances in diagnosis and management

Recent studies have shown that non-operative interventions such as percutaneous ultrasound guided alcohol injection and trans-arterial oily chemo-embolization may offer a prognosis comparable with that of hepatectomy in strictly selected patients.

Care, however, should be exercised in interpreting these results as none of the available reports were controlled and all were retrospective in nature.

Socioeconomic factors limit the use of liver transplantation in Asia.

While results of orthotopic liver transplantation appear promising with vigorous peri-operative chemotherapy, its feasibility in Asia is likely to be limited due to socioeconomic constraints.

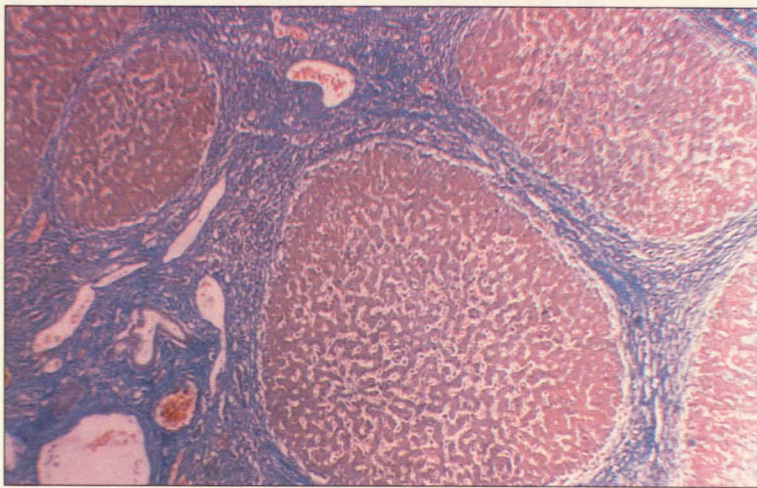
For most surgeons, hepatic resection remains the only proven treatment which may offer these patients a realistic chance of long-term survival.

Perioperative management

The potential benefit obtained from aggressive liver resection is often offset by the high post-operative morbidity and mortality rates. This has certainly been the case in the past.

An early report of our experience with 150 liver resections at the Queen Mary Hospital in Hong Kong in the '70s showed a hospital mortality rate of 20%.

Recently, however, results published on liver resection for HCC have greatly improved.



Liver cirrhosis

We have recently audited our results of liver resections carried out for HCC over a period of 22 years, up to the end of January, 1994.

During the study period, 343 (17.4%) of 1975 patients who had their primary liver cancer managed at our department underwent successful liver resection.

There remained a clear male predominance (297 males: 46 females) with a mean age of 53.4 years (range: 21 to 89 years). This had been previously noted.

Contrary to the experience in Japan where hepatitis B antigen was found in about one quarter of patients, 76% of our patients had positive serum.

Even though cirrhosis was prevalent among our patients (73%), a major liver resection (three or more Couinaud's segments) was often required since 78% of them had a large tumor (5 cm or over in diameter).

Based on the surgical technique employed, our results were divided into three different time periods: before 1987, 1987 to 1991 and 1992 to present.

Despite a significant increase in our resectability rate to 23% in the last two years, there was a clear improvement in the immediate postoperative outcome (Table 1).

Our current hospital mortality rate is only 6%.

The extent of liver resection and number of hospital deaths are shown in Table 2.

Preoperative assessment

Resectability is determined by the anatomical extent of disease and liver function.

While a hepatic and superior mesenteric angiogram is mandatory prior to surgery, computed tomography is being increasingly used.

Selective arterial injection of Lipiodol, an oily contrast medium, followed by computed tomography 10 to 14 days later is used extensively in cases where the diagnosis is uncertain and to detect occult lesions elsewhere in the liver.

Since 1987, the risk of post-operative liver failure has been assessed by both the function and physical volume of the proposed liver remnant.

Indocyanine green retention rate (normal: < 15% at 15 minutes) has been used to evaluate the hepatic reserve. The volume of the proposed hepatic remnant is determined by computed tomography.

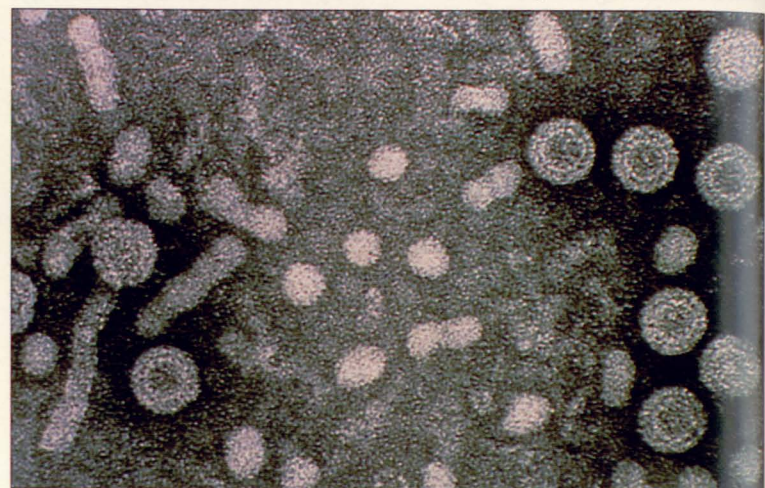
A diagnosis of HCC would be based primarily on a characteristic angiography and an elevated alpha fetoprotein (AFP) titer.

As there is a definite risk of seeding along the needle tract, the use of fine needle aspiration cytology is reserved for selected patients with an uncertain diagnosis. Histological confirmation is now rarely used for patients with resectable disease.

Operative techniques

In addition to our pre-operative evaluation, surgical techniques such as the choice of incision, the means of parenchymal transection and the mode of vascular control during the procedure continue to develop.

While a thoracotomy was



Hepatitis B virus

used extensively in the past, especially for the right hepatic resection, a bilateral subcostal incision, with or without a sternal extension, has been used since 1992 irrespective of the lateralization of lesion.

Intraoperative ultrasound has become an integral part of the operation as it helps to determine the extent of liver resection required based on the relationship between the lesion and the adjacent hepatic veins.

In addition, the course of the middle hepatic vein would be marked on the liver capsule when a major hepatectomy has been decided.

For segmental resection, methylene blue solution is injected into the segmental portal vein branch.

The boundary of the liver segment injected will become apparent on the liver capsule and thus allow an accurate segmental resection.

Success depends on good technological support and perioperative management.

After initial hilar control of the inflow vascular structures, liver transection can be carried out cautiously using an ultrasonic dissector. Minor oozing from the raw surface is controlled by an argon beam coagulator.

Occasionally, finger fracture, or a pair of artery forceps, can be

used to complete the final part of the resection. Portal clamping (Pringle's maneuver) is used with decreasing frequency, as in most instances the hepatic veins are the source of bleeding.

Furthermore, a transient warm ischemia might adversely affect postoperative recovery of liver function.

Occult bile leakage is ruled out routinely by injecting a diluted methylene blue solution via the cystic duct of the resected fragment.

All patients are ventilated for at least 12 hours in the immediate postoperative period. Abdominal drains are inserted as a routine.

Many factors may have contributed to our recent success, including better technological support and improved perioperative management.

Multivariate analysis verified our previous contention that patients with spontaneous ruptured tumor should be managed by trans-arterial embolization, especially when the diagnosis is established before surgery.

Even when a patient with an acute abdomen is explored, a hepatic artery ligation should be performed instead of an emergency hepatic resection, since the latter carries a formidable mortality rate despite offering a comparable chance of hemostasis.

For cirrhotic patients undergoing major liver resection, perioperative nutritional supplement with parental branch-chained amino-acid (one week preoperatively continued for one week postoperatively) was found to be helpful.

In our recent randomized controlled trial of 124 patients with HCC undergoing hepatectomy, additional nutritional support resulted in less weight loss and better preservation of liver function following resection.

Long-term management

The overall one-, three-, and five-year survival rates of all 343 patients undergoing liver resection were 60%, 33% and 24%, respectively, after all hospital deaths were excluded.

Further stratification of data, according to the period of management, before or after 1987, showed a significant difference in prognosis, with the median survival time doubled in recent years.

Survival rates after 1987 were 68%, 44% and 35%, respectively.

The major contributory factor to the improved outcome is more effective management of those with proven recurrent disease.

Although the disease-free interval remained comparable throughout our study, the one-, three- and five-year survival after recurrence was documented as increased from 35%, 15% and 9%, respectively before 1987 to 36%, 23% and 23%, respectively in recent years.

Postoperative follow-up

Early and effective treatment of intrahepatic recurrences probably accounts for the improvement.

After successful surgery, all patients are followed-up with a combination of serum AFP measurement and percutaneous ultrasound at monthly intervals for the first year and every two to four months thereafter.

Hepatic arteriography, or in equivocal cases, computed tomography after Lipiodol injection, would be used for localization if a recurrence is suspected.

Management of recurrent disease

The management of patients with recurrent disease depends on the number, location and the residual hepatic function.

The experience at Queen Mary Hospital with re-resection of intrahepatic recurrences is limited, as most patients had already undergone major liver resection and had underlying cirrhosis.

Nevertheless, we believe that aggressive surgery is worthwhile, as even in patients with isolated extra-hepatic disease, successful resection offers a better prognosis for these selected cases.

In the presence of multiple intrahepatic recurrent disease, trans-arterial chemo-embolization is the treatment of choice.

After selective cannulation of the hepatic arterial branch supplying the tumor-bearing lobe of the liver, an emulsion of Lipiodol and cisplatin is injected, followed by embolization with gel-foam.

Side-effects are negligible, although fever is common following the procedure.

The procedure is repeated once every two to three months.

Our enthusiasm for inserting a subcutaneous port as an atraumatic access to the hepatic vasculature for repeated angiographic studies, and regional chemotherapy when necessary, has been dampened by the frequent occlusion and inability of embolization via the system.

Whenever the lesions are small in size (less than 4 cm) or in number (less than 4), and readily apparent on transabdominal percutaneous ultrasound, alcohol injection is considered.

Unfortunately, little progress has been made for patients with widespread systemic disease.

Clinical studies suggest that administration of doxorubicin as a single agent is as effective as any other combination.

Future prospects

Based on the experience at Queen Mary Hospital, better management of patients with resectable HCC depends on the successful cooperation between the surgeons, radiologists and medical oncologists.

Studies are ongoing to further improve results.

Prevention of frequent recurrences is one area on which we have focused.

With technical advances, the use of laparoscopy and laparoscopic ultrasound performed immediately before a formal laparotomy has been helpful for various primary and metastatic liver tumors.

Patients should be spared unnecessary exploration.

Preliminary analysis of the initial 42 patients who were enrolled in our ongoing prospective study suggests that patients could be spared unnecessary exploration despite thorough preoperative imaging studies.

Moreover, the extent of liver resection required was altered after a visual assessment of the size of the liver remnant, or detection of occult lesions elsewhere in the liver or inside the major vessels.

The value of postoperative adjuvant chemotherapy is controversial.

Our previous data on patients with large HCC failed to demonstrate any benefit.

Recent retrospective data, however, suggests that either systemic, oral or regional chemotherapy is useful.

A prospective randomized trial has been in progress since 1990 using a combination of

Table I. Hepatectomy for patients with hepatocellular carcinoma: Results at Queen Mary Hospital, 1972-1994

	Before 1987 (n=149)	1987 - 1991 (n=128)	1992 to Present (n=66)	P-Value
Resectability rate (%)	14	20	23	<0.003
Complication rate (%)	73	52	32	<0.001
30-day mortality rate (%)	14	9.4	4.5	NS
Hospital mortality rate (%)	21.5	14.8	6	<0.02

Table II. Extent and results of hepatectomy for patients with hepatocellular carcinoma

Extent	Procedure	Before 1987 (n=149)	1987 - 1991 (n=128)	1992 to present (n=66)
Major	Rt. hepatectomy	59 (14)	53 (8)	23 (3)
	Rt. extended hepatectomy	20 (4)	25 (6)	15 (1)
	Lt. hepatectomy	29 (7)	10 (0)	3 (0)
	Lt. extended hepatectomy	5 (0)	3 (1)	5 (0)
Minor	Lt. lateral segmentectomy	11 (4)	10 (1)	6 (0)
	Non-anatomical resection	25 (3)	27 (3)	14 (0)

() No. of hospital deaths

systemic doxorubicin and regional cisplatin as an emulsion with an iodized oil.

It is hoped the information generated from this ongoing study will enable clinicians to further improve the survival of patients with HCC. ♦



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Edited by Dr Cindy L K Lam, MB BS(HK), FRCGP(UK), General Practice Unit, Department of Medicine, University of Hong Kong.

Q CME QUIZ

answers on inside back cover

- | | T | F |
|--|--------------------------|--------------------------|
| 1. Hepatocellular carcinoma (HCC) can be diagnosed by a characteristic angiogram and raised alpha fetoprotein (AFP) titer. | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. In the presence of an acute abdomen, emergency hepatic resection should be performed. | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Transarterial chemo-embolization is the preferred treatment for multiple intrahepatic recurrent disease. | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Adjuvant chemotherapy after hepatic resection is undoubtedly beneficial. | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. Aggressive surgery should be avoided in patients with recurrent disease. | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. Hepatic resection is best performed via thoracotomy. | <input type="checkbox"/> | <input type="checkbox"/> |

Please see next page for Erratum

COMMENTARY

Recently, more than 200 medical students from 10 Asian countries met in Hong Kong for the 16th Asian Medical Students' Conference organized by the Asian Medical Students' Association of Hong Kong. The theme of the conference was "Lifestyle and Health" and we found it very interesting to discuss with others the impact our cultural backgrounds and daily-life practices have on our health. We concluded that although lifestyle is one of the most important elements affecting our health — social, economic and even political factors also play a role.

We also noted in that many Asian countries where the standard of living is improving, the major health problems are shifting from infectious diseases to diseases of affluence. The best way to combat these "sleeping diseases" is to educate the public.

Sometimes physicians have little impact promoting health messages during a doctor-patient consultation. Government action, such as undertaking large-scale health campaigns and passing legislation restricting cigarette sales and advertising, is often more fruitful. Many Asian governments have already taken such action.

Medical students are playing a role in public education as well. We have organized a wide variety of exhibitions, talks and publications to arouse public awareness of different health issues.

Each country faces particular problems which are of concern to doctors. Those of us from Asia agreed that people should be alerted to parts of their traditional diet that are now known to be harmful. For example, we must educate the public on the relationship between highly salted or preserved food and nasopharyngeal cancer, gastric carcinoma and heart disease. People should also be warned about the effects of stress, cigarette smoking and overuse of NSAIDS, and their relationship to ulcers.

Indonesian, Malaysian and Thai delegates pointed out that although their countries are still battling infectious diseases and malnutrition-diabetes, cardiovascular disease and overnutrition are increasing and threatening to become significant problems.

In other countries, particularly Japan, the aging society is a major health issue. The cultural norm that the aged should be supported by their family has resulted in many elderly becoming dependent and unmotivated. It is necessary to promote the benefits of activity and exercise to this age group.

Christine Wat Sze Kee
Chairperson of the Asian Medical Students' Association of Hong Kong

QUESTION & ANSWER

Q:

In order to free Indonesia from poliomyelitis, the Minister of Health has declared that all children under five years of age should be given poliomyelitis vaccine. A mass-immunization campaign is scheduled for September 13 and October 18, 1995.

- Will children who have already had three polio vaccines during their first year and a booster in their second year benefit from this campaign?
- What influence do oral corticosteroids have on immunization as a whole and poliomyelitis and hepatitis vaccinations in particular?

We have two categories of children on corticosteroid treatment. The first category takes low maintenance doses orally over a long-term period. The second category is on short-term treatment with high doses of prednisone.

- How do corticosteroids interfere with the immunization process (when using attenuated or the very expensive killed vaccines)?
- What are the general guidelines for infants and children who are on oral corticosteroids but require universal immunization?

Dr Muherman Harun
St Carolus Hospital, Jakarta

A:

Children who have already completed their polio vaccination during the first year and had a booster in the second year of life will still need a booster between four to six years of age. An extra dose of oral polio vaccine will certainly do no harm to such children and may indeed contribute to the national effort in eradicating poliomyelitis through immunization of some of the contacts of the vaccinated children.

Regarding the influence of oral corticosteroids on immunization, the the American Academy of Pediatrics recommends that children treated with corticosteroids be categorized as follows :

1. Previously healthy children who are on a short-term (less than two weeks), low to moderate daily maintenance dose of systemic corticosteroids; or a low to moderate dose, long-term, alternate-day treatment with short acting systemic corticosteroids for a condition which, in itself, is not associated with a compromised immune system.

These children can receive live virus vaccines. Topical steroids usually do not result in immunosuppression that would contraindicate live virus vaccines. However, live virus vaccines should be avoided if immunosuppression results from prolonged topical application.

2. Healthy children treated with large amounts of systemic corticosteroids.

These children should not receive live virus vaccine. The immunosuppressive efforts of steroid treatment is quite variable. It is considered that a prednisone dose equivalent to, or greater than, either 2 mg/kg of body weight or 20 mg per day, will raise concern about the safety of immunization with live virus vaccines at that time.

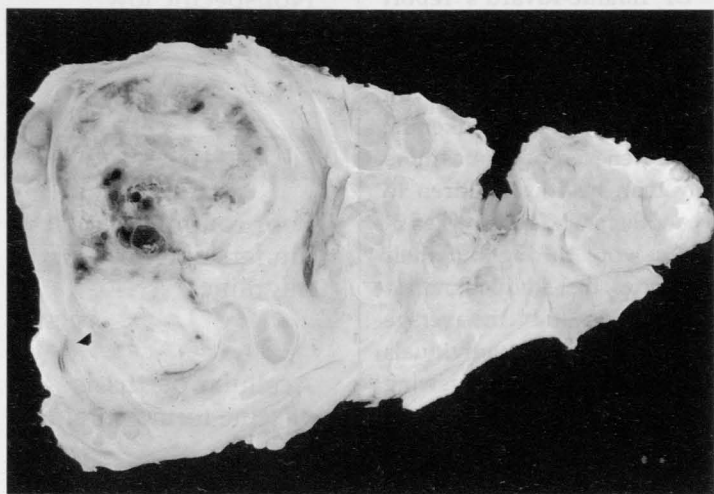
These children can obviously receive the killed virus vaccines with no risk of vaccine-associated poliomyelitis.

Hepatitis B vaccines are component vaccines and therefore are not contraindicated even in children who are treated with large amounts of systemic corticosteroids.

However, the immune responses to immunization may not be optimal due to the immunosuppression. The ability to develop a quantitatively normal immune response usually returns between three months and a year after discontinuing immunosuppressive treatment. Therefore, if it is possible, it may be wise to delay immunization, even with inactivated vaccines, in immunosuppressed children until they are off the immunosuppressive therapy for at least three months.

Dr YL Lau
University of Hong Kong

Q PATHOLOGY QUIZ



answers on inside back cover

A 23-year-old woman presented with a right loin mass which had been present since she was young. It had progressively increased in size and warranted surgical excision.

1. What is the architecture of the lesion?
2. What is your most likely diagnosis?
3. What complication can you see in this lesion?
4. What else would you look at in this patient?

Compiled by Dr John Nicholls, University of Hong Kong, Department of Pathology, Queen Mary Hospital, Hong Kong.

Mistaken identity

In the August Continuing Medical Education article "Surgical treatment of hepatocellular carcinoma," we inadvertently published a photo of Dr Edward CL Lai, of the University of Hong Kong's Department of Medicine, instead of a photo of the author Dr Edward CS Lai, of the University of Hong Kong's Department of Surgery. We apologize for the error.

Editor

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Asian Medical News

Published and printed in Hong Kong by MediMedia Asia, under license from Medical Tribune. 8th Floor Pacific Plaza, 410 Des Voeux Rd West, Hong Kong. Tel: (852) 2559 5888 Fax: (852) 2559 6910 e-mail: mmamn@hk.linkage.net

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Distributed on a controlled basis in Southeast Asia. Also available on subscription at US\$24 per annum.

Philippines edition entered as second-class mail at the Makati Central Post Office under Permit #302, dated 12 Feb 1992.

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Subscription copy, not for resale ISSN 0250-3328

