Interdepartmental Case Report

Novel Aspects in The Management of Hepatocellular Carcinoma

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Abstract : **Hepatocellular carcinoma (HCC) is one of the common cancers in Thailand which usually develops on a background of cirrhosis. We report a multimodal approach to the management of HCC. Though surgical treatment is the only opportunity for curing HCC, it is feasible only in a minority of patients. Various non-surgical treatment modalities have been developed and used extensively, but their efficacies are far from satisfaction and the prospect for the development of more effective treatment is dismal. Multidisciplinary treatment such as the combination of transcatheter oily chemoembolization and percutaneous ethanol injection appears to be the current trend of management for nonresectable HCC, and improvement in survival can be achieved compared to single mode treatment. Portal vein embolization is useful in patient in need of wide hepatectomy to induce pre-operative hypertrophy of future remnant liver, which would have been insufficient for safe resection. Moreover, intra-arterial 131-Iodine-Lipiodol given after curative resection significantly decreased the rate of recurrence and increased disease-free and overall survival in patients with HCC.**

เรื่องย่อ : **แนวทางการรักษาแบบใหม่ในโรคมะเร็งตับ**

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มะเร็งตับเป็นโรคมะเร็งที่พบได้บ่อยโรคหนึ่งในประเทศไทย รายงานผู้ป่วยโรคมะเร็งตับ 1 รายที่ได้รับการรักษาแบบสหสาขา แม้ว่าการผ่าตัดรักษามะเร็งตับจะเป็นการรักษาวิธีเดียวที่หวังผลหายขาดได้ แต่การรักษาด้วยการผ่าตัดก็สามารถทำได้ในผู้ป่วยเพียงส่วนน้อย เนื่องจากโรคมะเร็งตับมักเกิดขึ้นในภาวะตับแข็ง ปัจจุบันมีการพัฒนาแนวทางการรักษาใหม่ ๆ โดยไม่ต้องอาศัยการผ่าตัดมากขึ้น เช่นการฉีดยาเคมีบำบัดผสมกับ Lipiodol ผ่านทางหลอดเลือดแดงที่เลี้ยงตับ และการฉีดแอลกอฮอล์เข้าสู่มะเร็งตับโดยผ่านผิวหนังซึ่งเป็นวิธีการรักษาที่ใช้กันอย่างแพร่

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หลาย เทคนิคการฉีดสารเพื่ออุดตันหลอดเลือดดำพอร์ตัล (portal vein embolization) เป็นวิธีการใหม่ที่ช่วยให้เกิดการโตขึ้นของตับส่วนที่เหลือ เพื่อให้เพียงพอสำหรับความอยู่รอดของผู้ป่วยหลังผ่าตัด นอกจากนี้การฉีดสารไอโอดีนกัมมันตภาพรังสีร่วมกับ Lipiodol เข้าสู่หลอดเลือดแดงตับก็สามารถลดอัตราการเกิดโรคซ้ำและเพิ่มระยะเวลาการอยู่รอดของผู้ป่วยมะเร็งตับให้มากขึ้นได้

INTRODUCTION

Hepatocellular carcinoma (HCC) is responsible for more than 4% of all cancer cases and is the third common cause of death from cancer throughout the world. About 70-90% of HCCs develop on a background of cirrhosis. The prognosis of HCC largely depends on the size of tumor, its rate of growth, its histological grade, the degree of cirrhotic change and the presence of underlying disease. Approximately 20% of all nodules less than 1 cm in diameter when first detected already show microscopic signs of intrahepatic metastasis (invasion of the fibrotic capsule or portal vein).[1] Hepatic resection is feasible only in a minority of patients due to local tumor spread and the severity of pre-existing cirrhosis. Various non-surgical treatment modalities have been developed and used extensively, but their efficacies are far from satisfaction and the prospect for the development of more effective treatment is dismal.

CASE REPORT

A 50 years old man was admitted to Siriraj Hospital with a liver mass detected by routine check-up. He had right upper quadrant pain for 1 year prior to admission without other abnormal symptoms including weight loss. He had no underlying disease but smoked heavily and consumed alcohol for 30 and 20 years respectively. His physical examination revealed normal temperature, PR 80/min regular, RR 16/min, BP 110/80 mmHg, no signs of chronic liver disease, liver enlargement 4 FB below xiphoid, firm in consistency, no tenderness and no superficial lymphadenopathy. Blood analysis showed no anemia and normal liver function except a mildly elevated alkaline phosphatase and gamma-glutamyltranspeptidase with a normal coagulogram. Moreover, alpha-fetoprotein was normal whereas hepatitis B surface antigen was positive. His computerized tomography (CT) showed a large heterogenous mass, 12x13 cm, at the right lobe of liver (segment VII & VIII) with suspected right portal vein involvement. The mass was also near to the right diaphragm and inferior vena cava. He underwent liver biopsy and the result showed hepatocellular carcinoma, with microtrabecular pattern and mixed hepatic clear cell type, Edmonson grade III/IV. His selective angiogram demonstrated an accessory of the right hepatic artery from the superior mesenteric artery which fed a hypervascular tumor mass in the right lobe of the liver (Figure 1A).

He underwent 5 courses of transcatheter oily chemoembolization (TOCE). Post TOCE demonstrated lipiodol staining in the whole tumor and a decrease in tumor vascularity of about 85-90% due to embolization (Figure 1B). Subsequent CT scans showed the lipiodol staining at the periphery of the tumor with a central necrotic portion (Figure 2A) and, importantly, a decrease in size of the tumor (Figure 2B). However, after the 5th TOCE, a selective angiogram demonstrated no definite residual arterial feeder and there were multiple small collateral arteries supplying the right lobe of liver (Figure 3A, 3B). There was a further collateral branch from the coeliac plexus running cranially to the right lobe supplying the tumor. Unfortunately, it could not be selectively catheterized. Therefore, the patient was transferred to the Department of Surgery for consideration of surgical excision.

He underwent surgical excision of the tumor. The right lobe was found to have hypotrophic change and the tumor at segment VII&VIII adhered to the right diaphragm. The left lobe of the liver showed micronodular cirrhotic change but no evidence of tumor nodules on intraoperative ultrasonography. Classical right hepatectomy was performed. The postoperative course was uneventful and he was

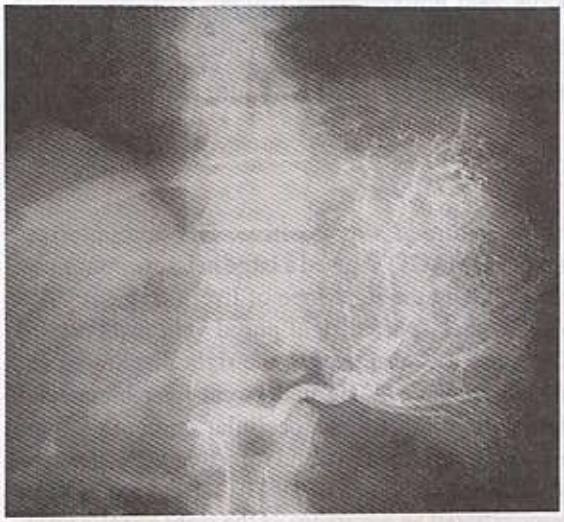

Figure 1. Selective catheterization of an accessory right hepatic artery from the superior mesenteric artery which showed hypervascularity and neovascularization of the tumor in the right lobe of liver.

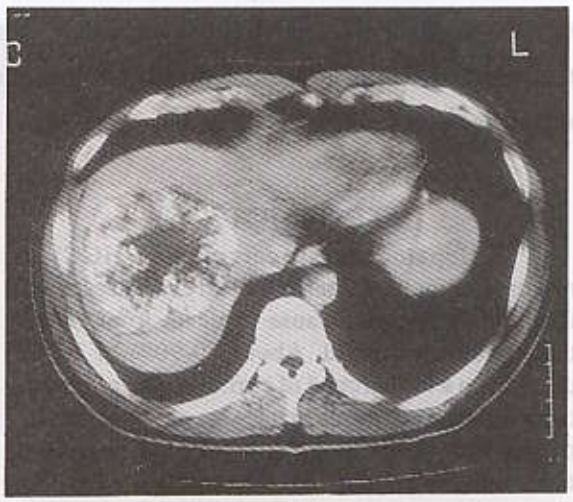

Figure 2A. Enhanced CT liver performed 3 months post 1st TOCE revealed Lipiodol staining at the periphery of the tumor in segment VIII with a central necrotic pattern.

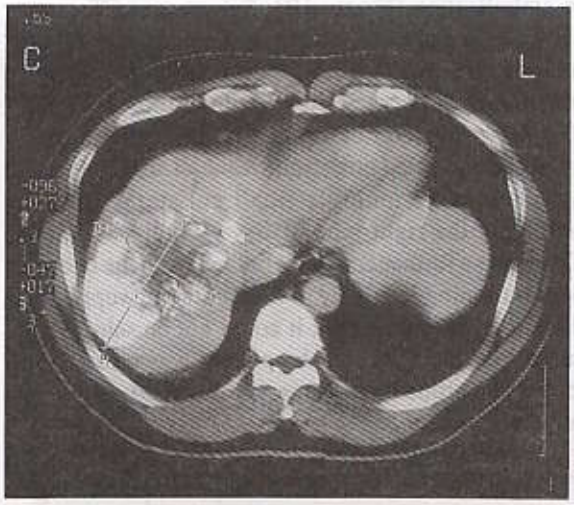

Figure 2B. CT liver with enhancement after 5th TOCE showed a decrease in size of the tumor from 8.0x8.5 to 6.6x8.4 cm.

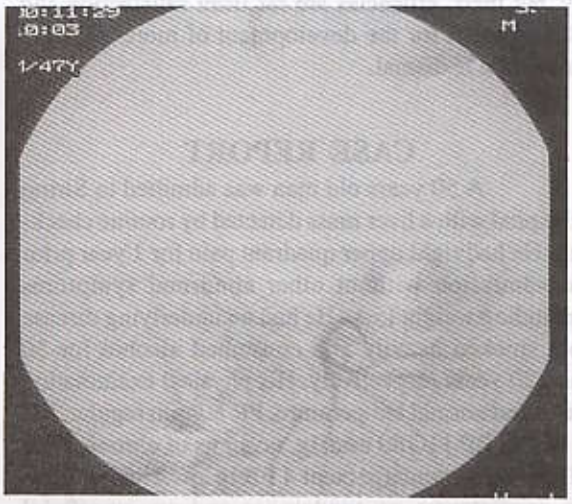

Figure 3A. Superior mesenteric artery arteriogram showed complete occlusion of the accessory right hepatic artery from multiple previous TOCE.

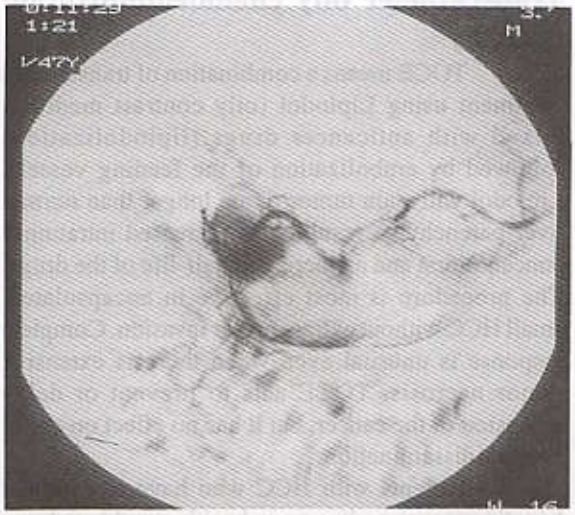

Figure 3B. Coeliac arteriography revealed small branches of the right hepatic artery which did not feed vessels.

discharged home on the 9th postoperative day. Pathology reported coagulation necrosis of a hepatocellular carcinoma with tumor emboli present.

DISCUSSION

Studies on the natural history of untreated HCC have shown that survival can reach 3 years in 12.8% of patients, but most patients die within 4 months of the onset of symptoms.[2] The following various multimodal approaches have been utilized in the management of HCC.

1. Liver resection with curative intent
   - 1.1 Partial hepatectomy
   - 1.2 Total hepatectomy with liver transplantation
2. Local treatment
   - 2.1 Cytoreductive surgery (debulking)
     1) palliative resection
     2) cryosurgery
     3) microwave surgery
   - 2.2 Percutaneous injection
     1) ethanol
     2) acetic acid
     3) radioactive isotopes
     4) chemotherapeutic agents
   - 2.3 Percutaneous microwave treatment
3. Hepatic artery transcatheter treatment
   - 3.1 Transarterial chemotherapy
   - 3.2 Transarterial embolization
   - 3.3 Transarterial chemoembolization
   - 3.4 Transarterial radioembolization (yttrium 90 microspheres or Lipiodol iodine 131)
4. Systemic treatment
   - 4.1 Chemotherapy
   - 4.2 Immunotherapy
   - 4.3 Chemoimmunotherapy
   - 4.4 Hormonal therapy
5. Supportive treatment

Surgical management

Surgery is the only treatment option which has the potential to cure HCC. Nevertheless, it is feasible only in a minority of patients due to local tumor spread and the severity of pre-existing cirrhosis. Indications for surgery are for cure, for diagnosis, prevention of mass effect (palliation), prevention of rupture, and complicated disease such as bleeding or functional tumor.

The disease, patient status, and surgeon are three main factors that should be considered when deciding on surgical treatment. Multicentric disease or disseminated disease such as malignant ascites, transcoelomic spread or distant metastases are contraindications for surgery. Resectability in cirrhotic patients is limited by the diminished functional reserve of the cirrhotic liver, with the attendant risks of intraoperative bleeding and postoperative liver failure. In the absence of cirrhosis, the tumor is usually diagnosed at a very late stage. The Child-Pugh classification has been used for the evaluation of the liver function. Normally, the extent of liver resection is carefully performed and limited in Child's class A and early class B. To date, indocya-

nine green (ICG) clearance is the only test which is useful to predict hospital mortality and survival in cirrhotic patients with hepatic resection. It is removed by the liver by a carrier-mediated mechanism and excreted unchanged into the bile.

With the improved understanding of Couinaud's segmental anatomy of the liver, the extent or resection varies from major (extended) right/left hepatectomy, segmentectomy to wedge resection of the tumor. However, as the dissemination of HCC occurs by retrograde invasion of distal portal branches, a curative resection should remove the entire parenchymal area supplied by its main portal branch. Advances in anesthetic techniques, vascular inflow control and maintenance of a low central venous pressure (CVP) during hepatectomy have been applied to reduce intraoperative blood loss in liver resection.

Prognostic factors associated with long-term survival after liver resection for HCC are size of tumor, cirrhosis, infiltrative growth, vascular invasion, TNM stage, intrahepatic metastases, multiple tumors, capsule formation, lymph node metastases and a surgical margin less than 1 cm. The last factor is the only factor that the surgeon can control. 1, 3, 5 and 10 years survival rates after liver resection for HCC are 58-100%, 28-88%, 11-76% and 19-26% respectively. 50-90% of postoperative death is due to recurrent disease.

Liver transplantation has become widely accepted as therapy for HCC when tumors are not suitable for resection because of anatomical restrictions (location, size or number of intrahepatic lesions) or functional impairment (underlying cirrhosis). For transplantation, the 3 years survival without recurrence in the case of small uninodular or binodular tumors (less than 3 cm) is significantly better than that for resection, 83% compared to 18%, respectively. However in terms of overall survival rates, resection and transplantation yield the same results (50% compared to 47%, respectively).[3] Moreover, the growth rate of HCC is accelerated with mean tumor doubling times of 37 days in recurrent tumors after transplantation, compared with 274 days in patients with recurrence after resection.[4]

Transcatheter oily chemoembolization (TOCE)

TOCE means a combination of transarterial treatment using Lipiodol (oily contrast medium) mixed with anticancer drugs (lipiodolization) followed by embolization of the feeding vessels. Lipiodol will stain tumor tissue longer than normal liver parenchyma resulting in increased intratumor concentration and an increased half-life of the drugs. The procedure is most effective in encapsulated, small HCC without extracapsular invasion. Complete response is unusual even when there is extensive tumor necrosis. TOCE acts to prevent or delay extension of the cancer, but it has no effect on extra-hepatic dissemination.

Patients with HCC who have insufficient hepatic reserve and/or poor health should undergo TOCE. Other indications for TOCE are pre-operative liver resection and preparation for liver transplantation. Complete portal thrombosis, major hepatic insufficiency (Child's class C or Okuda's class III) and severe renal insufficiency are contraindica-tions for TOCE except when active intraperitoneal bleeding from the tumor has occurred. Lipiodolization can still be performed when there is portal thrombosis.

Superselective chemoembolization should be done when surgery and conventional TOCE are contraindicated, the location of the tumor hinders application of percutaneous tumor ablation, the tumor is greater than 3 cm in size, the tumor is hypervascular and the masses are located in only 2-3 subsegments.

Factors predictive of survival after TOCE are tumor size and location, portal vein invasion, hepatic function reservoir, the treatment modalities used, the presence of extrahepatic metastasis and resectability. Complications after TOCE include fever, nausea and vomiting, abdominal pain, deterioration of hepatic function to hepatic failure, hepatic infarction, intrahepatic biloma, distal embolization and postembolization syndrome. Follow up is needed in the patients undergoing TOCE. Tumor markers and liver function tests should be measured every 3 months, imaging (CT or MRI)

every 6-8 weeks in order to evaluate the response to treatment. Repeated TOCE every 6-8 weeks is also recommended.

Percutaneous tumor ablation

This procedure includes intralesional injection of absolute ethanol, acetic acid, hot saline; heating using radiofrequency, laser, microwave; and freezing such as cryotherapy.[5]

Percutaneous Ethanol Injection (PEI)

Current indications for PEI are HCC and hepatic metastasis. The limitations of PEI are that the tumor should be less than 5 cm in its greatest dimension and there should be less than 3 lesions. This is because ethanol may not diffuse through larger tumors. Contraindications to PEI include extrahepatic metastasis and irreversible coagulopathy. The mechanism of action of alcohol after diffusing into tumor cellsis producing immediate coagulation necrosis (due to the effects of cellular dehydration and protein denaturation) followed by fibrosis and small vessel thrombosis.[6] All the factors can lead to tumor cell death.

The total amount of alcohol injected is calculated by $V=4/3\pi(r+0.5)$,[3] where V is the volume of ethanol and r is the radius of the lesion measured in mm. The addition of 0.5 to the radius is designed to achieve the necrosis of a rim of nontumorous tissue around the tumor. It has been demonstrated that volumes up to 40 ml per session can be used safely. Multiple sessions, twice a week are recommended. Some authors have also proposed a single PEI session with a general anesthetic in patients with large or multiple HCC. The therapeutic efficacy of PEI is assessed with dual-phase spiral CT 4 months after treatment. Tumor markers are useful for evaluating the treatment response.

The complications of PEI are fever, pain, alcohol intoxication, pneumo/hemothorax, intraperitoneal bleeding and liver abscess. Tumor seeding occurs rarely. The limitations are a non-encapsulated tumor, deep location and large tumor. Survival rates are better when the patients have good liver function, have small lesions (< 5 cm), and have fewer than 3 lesions.

Combined TOCE and PEI

Usually performed 2-4 weeks apart, TOCE followed by PEI. Tumor necrosis from TOCE produces good ethanol diffusion. Decreased vascularity results in a diminished wash out effect of ethanol. The procedures increased survival rate and decreased recurrence rate in patients with a tumor less than 5 cm in size.

Portal vein embolization (PVE)

The procedure is utilized to induce hepatic lobe hypertrophy before surgery. It is useful in patient in need of wide hepatectomy to induce preoperative hypertrophy of the future remnant liver (FRL) which would have been insufficient for safe resection. Because portal blood flow has a hypertrophic property,[7] we redistribute portal flow in an attempt to induce hypertrophy of an initially insufficient FRL and eventually widen the possibilities of curative resection. Access to the portal vein is achieved by means of percutaneous placement of a 5 French size catheter into the right/left portal vein *via* portal puncture under sonographic and fluoroscopic guidance. After placement of catheter tip in the main portal trunk, digital subtraction portography is performed to identify individual branches of anatomic variations. Portal embolization is undertaken once normal portal venous blood supply to the liver is evident. The branch of the portal vein and its ramifications occluded with gelatin sponges (Gelfoam) and polyvinyl alcohol (Ivalon). Baere, et al. embolized the portal vein with *N*-butyl-2-cyanoacrylate (Histoacryl) mixed with iodized oil (Lipiodol) or thrombin and gelatin sponges.[8]

Embolization efficiency is assessed with post-PVE portography and CT scan for volumetric measurement of the entire liver and FRL is done immediately before PVE and 4-6 weeks later.

Portal vein embolization is a safe and well-tolerated procedure that induces valuable hypertrophy of the unembolized segments of the liver.

Adjuvant intra-arterial 131-Iodine-labelled Lipiodol for resectable HCC

Lipiodol, a stable fatty acid ethyl ester derived from poppyseed oil, contain 38% iodine by weight and is retained by HCC after intra-arterial injection.[9] This high iodine content enables Lipiodol to be converted to radioactive 131-Iodine-labelled Lipiodol through an atom-to-atom exchange reaction.[10] Intra-arterial 131-Iodine-Lipiodol has been used to treat inoperable HCC and is well tolerated and effective in small tumor.[11]

Resection of HCC is potentially curative, but local recurrence is common. In the study, we used one dose or 60 milliCuries or 1850 MBq of radioactive 131-Iodine-labelled Lipiodol for postoperative adjuvant intra-arterial hepatic injection to reduce the rate of local recurrence and increase disease-free and overall survival.

In HCC patient, there is a high incidence and early occurrence of local relapse because of microscopic disease in the liver remnant after resection. Since 131-Iodine-Lipiodol has few toxic effects and is effective in the treatment of HCC. So this agent could be used as an adjuvant treatment after surgery. We injected one dose (60 mCi) of 131-Iodine-Lipiodol intra-hepatic artery in patients who underwent curative resection for small HCC. According to Lau, et al.[12] the recurrence rate during a follow up of 34.6 months was 28.5% in the intra-arterial 131-Iodine-Lipiodol group and 57.2% in the control group. Median disease-free survival in the treatment and control groups were 57.2 and 13.6 months, respectively ($p = 0.037$). 3 years overall survival in the treatment and control groups were 86.4% and 46.3%, respectively ($p = 0.01$).

In conclusion, one 1850 MBq dose of intra-arterial 131-Iodine-Lipiodol given after curative resection significantly decreased the rate of recurrence and increased disease-free and overall survival in patients with HCC.

Nonsurgical and nonlocoregional management

Prolonged survival in patients with HCC is best achieved by either surgical removal or liver transplantation. However, very small proportions of patients with HCC are suitable for such treatment. The reasons that limit patients from curative treatment are advanced HCC, presence of cirrhosis, presence of chronic viral hepatitis, and co-morbid diseases. Therefore, nonsurgical approaches must be considered to prolong survival and improve the quality of life in these patients. General manage-ment aims to improve nutritional status, control portal hypertension, and reduce cancer pain.

Most HCCs are multifocal especially when associated with chronic viral hepatitis (either hepatitis B or C). Systemic chemotherapy may show an advantage for controlling such advanced and multifocal disease. Doxorubicin, as a single agent and many combinations of drugs such as 5-FU, alfa-interferon and cisplatin, may induce at least partial remission and prolong survival. Many new drugs and pro-drug combinations are under intensive investiga-tion with a greater potency against HCC but are less toxic.

Estrogen receptors can be detected in as many as one third of HCC patients. Tamoxifen alone or in combination failed to demonstrate any benefit on survival. A recent study using megestrol showed prolongation of survival in estrogen receptor positive HCC patients.[13]

Use of antiangiogenic agents in an animal model resulted in a reduction of HCC. An initial trial with thalidomide failed to demonstrate such benefit. Octreotide, a somatostatin analogue that possesses antimitotic activity increased the median survival from 4 months to 13 months in one study when used at 250 mg twice daily.[14] Gene therapy, immunothe-rapy, tumor vaccine and induction of apoptosis are potential future treatments.

CONCLUSION

We demonstrate a case with a large HCC in the right lobe of the liver who underwent chemoem-bolization and subsequent surgical resection. Surgery is the treatment of choice in this disease. However, combined surgical, medical and intervention radiology management provide more options and a better clinical outcome for HCC.

COMMENT

Clinical Professor Chana Sathornkich
Chairman, Department of Surgery

This case report of HCC has been successfully treated by a multimodal approach. Improvement in the understanding of liver anatomy, physiology, surgical techniques and advances in intervention radiology provide a chance to help patients suffering from this disease. To date, about 25% of treated HCC patient can survive up to 10 years. However, early detection and early resection may afford a permanent cure or a worthwhile prolongation of survival. The dismal outcome of this disease is largely due to difficulties in detecting the asymptomatic precursor lesions and early stages of HCC, therefore the majority of HCCs are not amenable to curative therapy at the time they are detected. Attempts to improve the outcome should be also aimed at earlier detection and prevention.

REFERENCES

1. Ebara M, Ohto M, Shinagawa T, et al. Natural history of minute hepatocellular carcinoma smaller than three centrimeters complicating cirrhosis. A study in 22 patients. Gastroenterology 1986; **90:** 289-298.
2. Nagasue N, Yukaya H, Hamada T, et al. The natural history of hepatocellular carcinoma. A study of 100 untreated cases. Cancer 1984; **54:** 1461-1465.
3. Bismuth H, Chiche L, Adam R, et al. Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. Ann Surg 1993; **218:** 145-151.
4. Yokoyama I, Sheahan DG, Carr B, et al. Clinicopathologic factors affecting patient survival and tumor recurrence after othotopic liver transplantation for hepatocellular carcinoma. Transplant Proc 1991; **23:** 2194-2196.
5. Caturelli E. Percutaneous ablative therapy for small hepatocellular carcinoma: radio-frequency or percutaneous ethanol injection? Radiology 2000; **216:** 304-306.
6. Lee MJ, Mueller PR, Dawson SL, et al. Percutaneous ethanol injection for the treatment of hepatic tumors: indications, mechanism of action, technique, and efficacy. Am J Roentgenol 1995; **164:** 215-220.
7. Starzl TE, Francavilla A, Halgrimson CG, et al. The origin, hormonal nature, and action of hepatotrophic substances in portal venous blood. Surg Gynecol Obstet 1973; **137:** 179-199.
8. de Baere T, Roche A, Vavasseur D, et al. Portal vein embolization: utility for inducing left hepatic lobe hypertrophy before surgery. Radiology 1993; **188:** 73-77.
9. Okayasu I, Hatakeyama S, Yoshida T, et al. Selective and persistent deposition and gradual drainage of iodized oil, Lipiodol in the hepatocellular carcinoma after injection into the feeding hepatic artery. Am J Clin Pathol 1988; **90:** 536-544.
10. Madsen MT, Park CH, Thakur ML. Dosimetry of iodine-131 ethiodol in the treatment of hepatoma. J Nucl Med 1988; **29:** 1038-1044.
11. Yoo HS, Park CH, Lee JT, et al. Small hepatocellular carcinoma: high dose internal radiation therapy with superselective intra-arterial injection of I-131-labeled Lipiodol. Cancer Chemother Pharmacol 1994; **33 Suppl:** S128-S133.
12. Lau WY, Leung TW, Ho SK, et al. Adjuvant intra-arterial iodine-131-labelled Lipiodol for resectable hepatocellular carcinoma: a prospective randomised trial. Lancet 1999; **353:** 797-801.
13. Villa E, Ferretti I, Grottola A, et al. Hormonal therapy with megestrol in inoperable hepatocellular carcinoma characterized by variant oestrogen receptors. Br J Cancer 2001; **84:** 881-885.
14. Kouroumalis E, Skordilis P, Thermos K, et al. Treatment of hepatocellular carcinoma with octreotide: a randomised controlled study. Gut 1998; **42:** 442-447.