Gigantic Hepatocellular Carcinoma, Treated by Transcatheter Oily Chemoembolization (TOCE) and Wedge Hepatic Resection

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Abstract

Four cases of gigantic hepatocellular carcinoma, considered by surgeons to be inoperable, were treated with repeated transcatheter chemoembolization (TOCE) until the serum alfafetoprotein reduced to normal or less than half of the original level or until the tumor reduced to less than half of the original size documented by CT scan and angiogram. Wedge hepatic resection was performed using ultrasonic dissector. Histologic section of the resected tumor mass revealed tumor necrosis. The extent of tumor necrosis was related to tumor size and corresponded inversely to the thickness of the tumor capsule. The survival periods were 48 to 108 months with only one to two episodes of recurrence during follow-up. Repeated wedge hepatic resection was performed successfully for recurrent cases.

Serum alfafetoprotein (AFP) is a very sensitive and reliable tumor marker for follow-up results and appears to be a sensitive indicator for tumor recurrence.

Key word : Gigantic Hepatocellular Carcinoma, Treatment

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Hepatocellular carcinoma (HCC) is common in Asian countries[1]. Its survival rate is not satisfactory. The median survival time in untreated patients is one to four months from the time of diagnosis[2-5]. Surgical resection, if feasible, provides the best results, but surgical management is limited by a low resectability rate (0-33%). This is attributed to multiple or both lobes involvement, gigantic size of the tumor, tumor in the hilar area or tumor presented with cirrhosis. The mortality

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rate related to surgical resection is as high as 10 per cent to 35 per cent[3]. There have been reports of using transcatheter oily chemoembolization (TOCE) preoperatively to decrease tumor bulk with large unresectable HCC[7]. With repeated TOCE to decrease tumor bulk, and tumor neovascularities, it is possible to convert unresectable tumor and prolong the patient's survival.

In this report, 4 patients with gigantic HCC documented clinically and by CT scan were treated preoperatively by TOCE followed by wedge hepatic resection. The degree of tumor necrosis estimated by histologic and gross tumor examination after surgical removal was studied. The relationship of capsule thickness of the tumor including tumor size to percentage of tumor necrosis was discussed. The serum alfafetoprotein (AFP) titers in follow-up cases were also thoroughly discussed.

MATERIAL AND METHOD

From May 1989 to November 1998, 4 patients who had been admitted for treatment were chosen as the subjects. All were male patients, aged 36 to 64 years old. The criteria of the subjects were patients with gigantic and single hepatocellular carcinoma. The tumors were demonstrated by CT scan of the upper abdomen and pathologically confirmed by liver biopsy prior to the treatment procedure. They were 10 to 18 centimeters in size, with three of them located at the right lobe of the liver, and only one patient had a huge tumor seen in the left lobe. All patients were in stage 2 disease by Okuda's classification[9] with mild elevated SGOT and SGPT with no ascites but had normal serum albumin and bilirubin. All patients except one (case 4 Table 1) were cirrhotic patients.

The serum HBsAg was positive in all patients. The clinical presentation including the follow-up result after treatment is summarized in Table 1. TOCE (Transcatheter oily chemembolization) was performed in all cases with selective catheterization of right, left or proper hepatic arteries feeding the tumor. 5 FU 500 milligram was infused through the feeding artery, followed by infusion of a fluid containing diluted mitomycin-C 20 milligram and lipiodol 10 ml (water-in-oil emulsion).

The tumor feeder arteries were finally embolized with gelfoam particles 1 x 1 mm in size until cessation of blood flow seen fluoroscopically. The patients were seen by a surgeon and radiologist in the outpatient clinic after being discharged with sequential examination of serum alfafetoprotein (case 1 and case 4) and CT scan of the upper abdomen monthly (all cases). Repeated TOCE was performed (6 weeks from the first TOCE) in cases in which the serum titer of AFP was high or CT

Table 1. Summarized the clinical presentation and follow-up after treatment of hepatocellular carcinoma.

Case number	1	2	3	4
Sex / age	M / 39	M / 36	M / 64	M / 46
Abdominal pain	+	+	-	+
Palpable mass	+	+	+	+
Weight loss	+	-	-	+
Cirrhosis	+	+	+	-
Staging (Okuda's)	2	2	2	2
HBs Ag	+	+	+	+
Tumor location	Right lobe	Right lobe	Left lobe	Right lobe
Tumor size (cm)				
Pre TOCE	10 x 7 x 8	14 x 12 x 13	16 x 18 x 17	10 x 9 x 8
Post last TOCE	4 x 6 x 6	9 x 9 x 8	5.5 x 5.6 x 5.4	3.5 x 4.5 x 4
Frequency of TOCE	4	2	3	1
Interval from TOCE to surgery (months)	7	1	1	2
Recurrent (months) from surgery	36	none	24	46
Recurrent rate	1	none	2	1
Survival (months) from first TOCE	48	48	108	53
Cause of dead	Loss follow up after 48 months follow up	Brain and lung metastasis	Rupture esophageal varices	Mitomycin-C toxicity

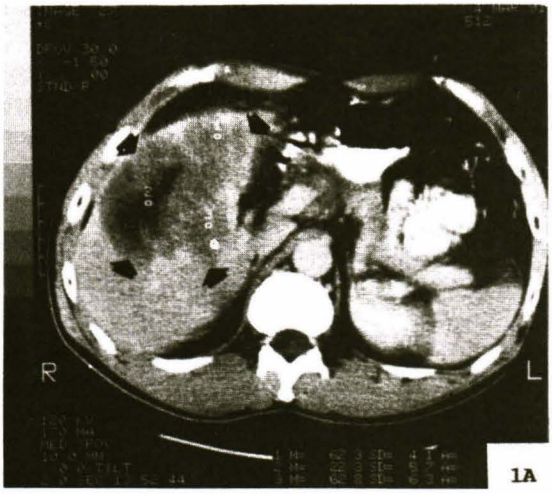


Fig. 1A. Case 1 contrast enhanced CT upper abdomen shows a large HCC right lobe liver measuring 10 x 7 x 8 centimeters in size (arrow).

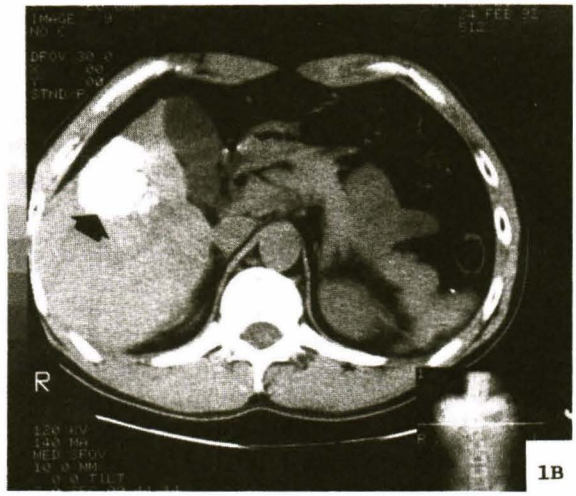


Fig. 1B. Same case as Fig. 1A, contrast enhanced CT upper abdomen after 4 times TOCE shows lipiodol retained in necrotic HCC at right lobe liver measuring 4 x 6 x 6 centimeters in size (arrow) which is markedly reduced in size and curative resection is technically feasible.

scan of the upper abdomen showed residual tumor (15). The time interval from the last TOCE to wedge hepatic resection of the tumor is suggested as follows :

1. When the tumor has decreased in size to 50 per cent of the original diameter seen from CT scan of the upper abdomen or angiogram (Fig. 1A, 1B, 1C).

2. When a marked decline of serum AFP is observed (case 1 Table 2).

3. When the side effect of TOCE has disappeared.

4. When CT scan of the upper abdomen indicates that curative resection of tumor is technically feasible.

Following wedge hepatic resection of the tumor, the patients were followed-up regularly with monthly serum alfafetoprotein and CT scan of the upper abdomen. Repeated TOCE or wedge hepatic resection was performed if residual or recurrent tumor occurred (case 3).

The long-term follow-up period was 9 years from the first TOCE (Table 1). The specimens obtained from the wedge hepatic resection were examined grossly for capsule thickness and for percentage of tumor necrosis measured on the largest tumor cross-sectional area which is summarized in Table 4.

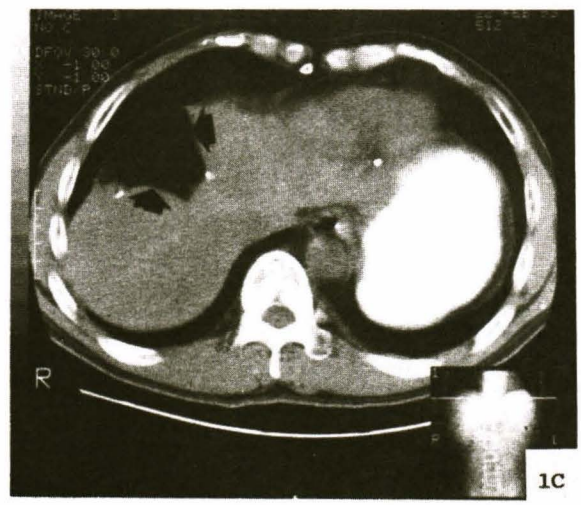


Fig. 1C. Same case as Fig. 1A, contrast enhanced CT upper abdomen after hepatic wedge resection of the tumor appears in Fig. 1B and the surgical defect is well demonstrated in CT scan (arrow).

Table 2. Serum AFP level in case 1 after treatment with TOCE with gradual decrease in level and becomes to be zero after surgery. The titer rising in follow-up after surgery correspond to recurrent HCC.

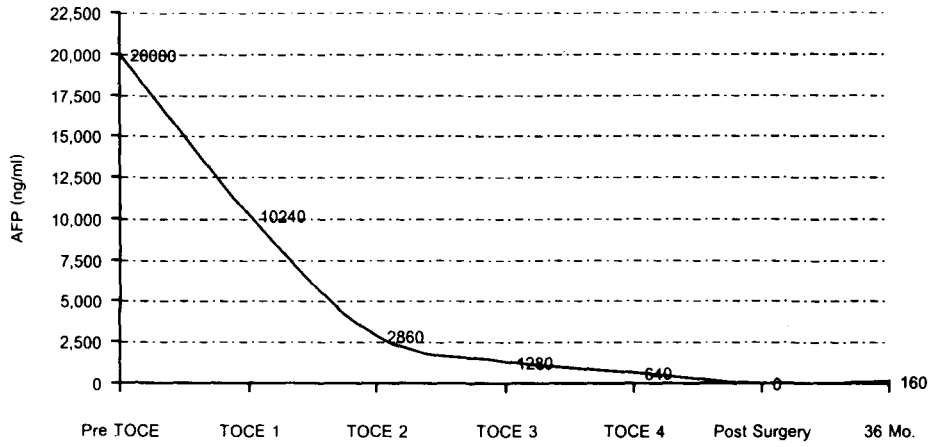
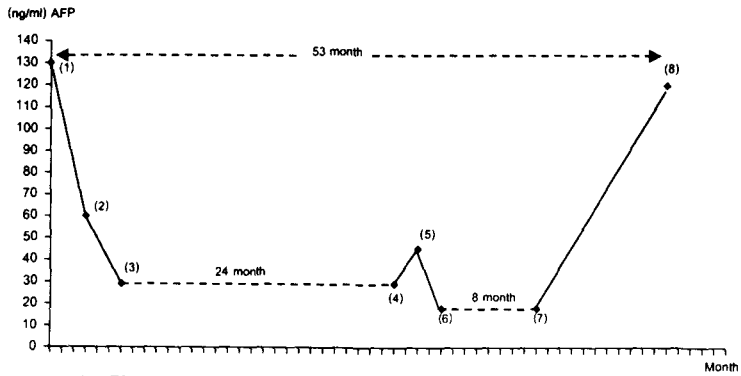


Table 3. Serum AFP level in case 4 after treatment with TOCE and surgery. Noted the AFP remain normal or high normal following surgery for 24 months, then the titer started rising (5) correspond to recurrent HCC documented by CT scan.



(1) TOCE done
(2) Wedge hepatic resection done
(3) Level of AFP decrease to this level and sustained for 2 years
(4) Started increase level of AFP corresponding to sign of recurrent HCC
(5) Segmentectomy of HCC done
(6) AFP decrease to this level and sustained for 8 months
(7) Start increase level of AFP represent recurrent HCC
(8) Patient expired from MTC intoxication

RESULT

The results of treatment and long-term follow-up are summarized in Table 1. The tumor masses were all decreased in size by more than 50 per cent prior to surgery. The gigantic size HCC such as in case 3 (16 x 18 x 17 centimeters) could be reduced to a small size tumor (5.5 x 5.6 x 5.4 centimeters) with TOCE 3 times seen in Fig. 2A and 2B.

Long-term follow-up revealed that one patient lived normally for 48 months (case 1), then failed to return for follow-up. One patient died

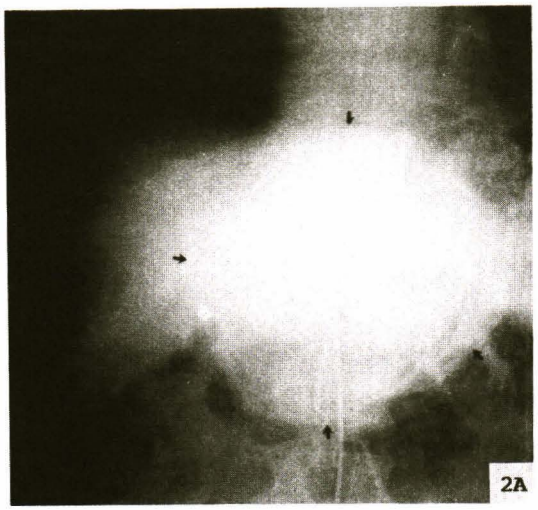


Fig. 2A. Case 3. Delay capillary phase of celiac angiogram demonstrats a huge tumor stain due to HCC in left lobe liver 16 x 18 x 17 centimeters in size (arrow).

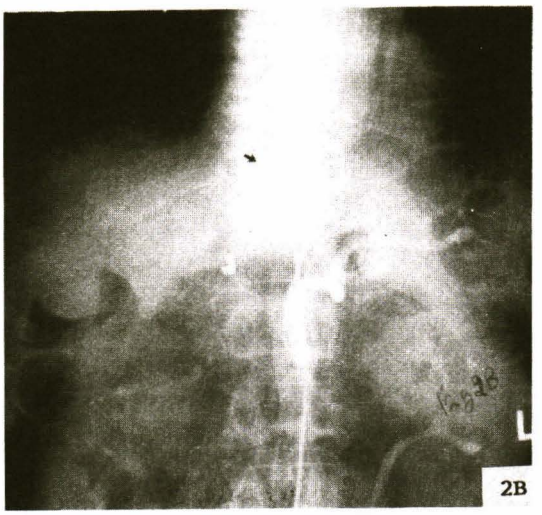


Fig. 2B. Follow-up celiac angiogram in case 3 Fig. 2A after last TOCE (TOCE 3 times) prior surgery shows lipiodol retained in necrotic tumor of left lobe which now measures only 5.5 x 5.6 x 5.4 centimeters (arrow). Note the left hepatic artery which was occluded by previous TOCE.

Table 4. Shows relationship of tumor capsules, size, to percentage of tumor necrosis after TOCE and wedge resection of hepatocellular carcinoma.

Case No.	Tumor size and location prior op.	Capsule thickness	Embolized artery	TOCE → op (months)	Result (percent necrosis)
1	Right lobe 4 x 6 x 6 (cm)	4 mm	Right hepatic	7	90
2	Right lobe 9 x 9 x 8 (cm)	2 mm extension outside capsule	Right hepatic	1	80
3	Left lobe 5.5 x 5.6 x 5.4 (cm)	4 mm	Left hepatic	1	95
4	Right lobe 3.5 x 4.5 x 4 (cm)	2 mm	Right hepatic	2	80

from brain and lung metastasis (case 2) this patient had grossly diaphragmatic extension on resected specimen. It is interesting to note that there was no hepatic recurrent HCC at the time of brain and lung metastasis. One patient survived for 53 months but eventually died from toxicity of chronic systemic administration of mitomycin-C high doses (case 4). It was surprising to see that one patient (case 3) survived and lived normally for 108 months after the first TOCE and finally died from ruptured esophageal varices. Although there were two episodes of recurrent HCC in case 3 and surgical wedge resection was done successfully.

Two of our patients had high levels of serum AFP and subsequent follow-up serum AFP was obtained as shown in Table 2 (case 1) and

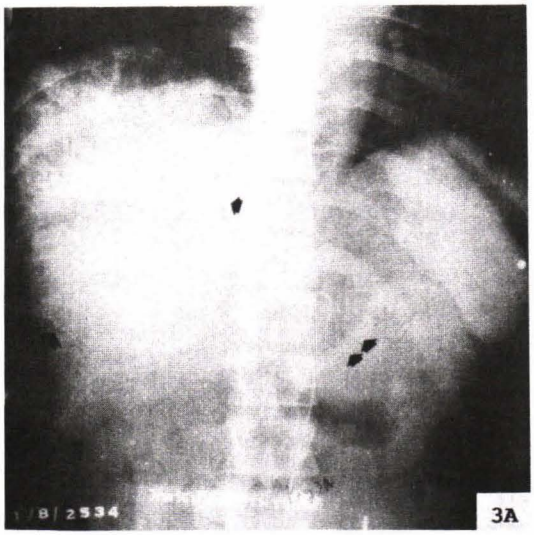


Fig. 3A. Case 2. Initial venous phase of celiac angiogram shows patency of portal vein (2 arrows) hypervascular HCC in right lobe liver 14 x 12 x 13 centimeters in size.

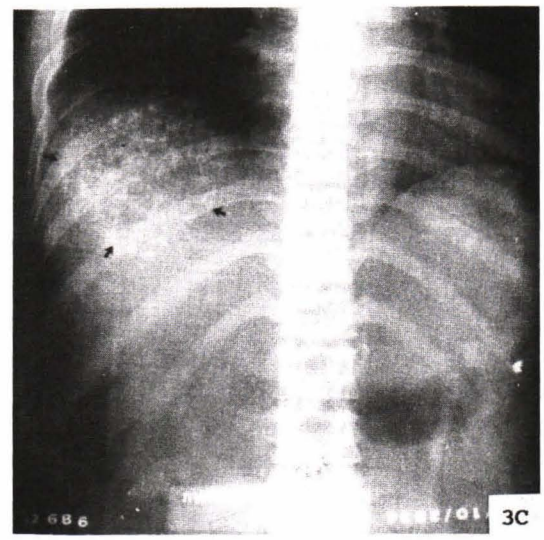


Fig. 3C. Same case as Fig. 3A. Plain film abdomen post second TOCE shows decrease in size of HCC with lipiodol stain (arrow).

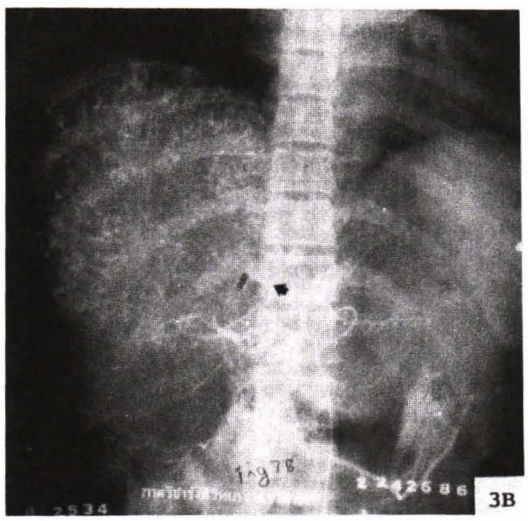


Fig. 3B. Same case as Fig. 3A post first TOCE shows retention of lipiodol in right lobe liver (arrow).

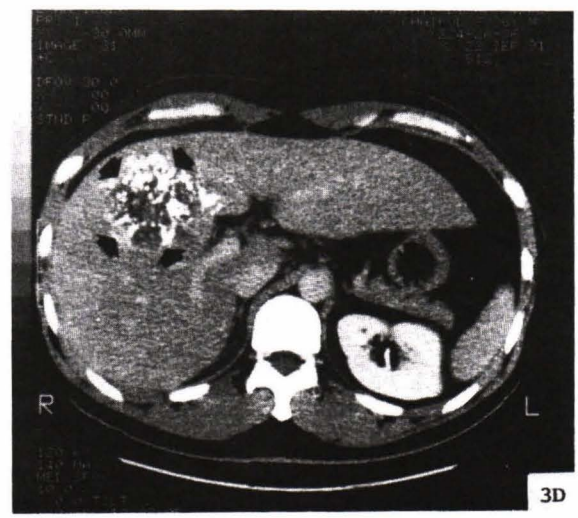


Fig. 3D. Same case as Fig. 3A, contrast enchanced CT scan after second TOCE prior to surgery shows decrease in size of HCC now technically feasible to be resected (arrow).

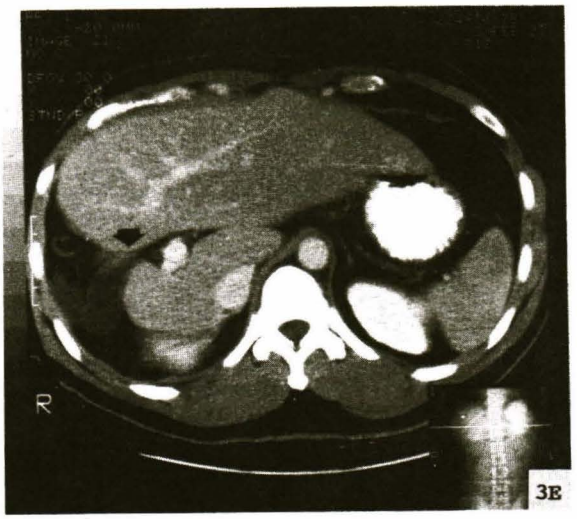


Fig. 3E. Follow-up contrast enhanced CT scan (same case as Fig. 3A) shows defect in right lobe from wedge hepatic resection (arrow). No residual tumor seen.

Note : some evidence of diaphragmatic extension suspected in angiogram (Fig. 3A, B, C), but not seen in CT scan in Fig. 3D.

Table 3 (case 4) which revealed that serum AFP is a sensitive and specific tumor marker to indicate tumor response and tumor recurrence as shown in both tables. The decreased serum AFP titer corresponded well to tumor response shown clinically and documented by CT scan of the upper abdomen. Its rising titer is a good indicator of recurrent tumor (Tables 2 and 3).

Table 4 shows a good correlation of tumor size and thickness of tumor capsule in relationship to the percentage of tumor necrosis. The smaller tumor after TOCE showed a higher percentage of tumor necrosis, the capsule thickness of 4 millimeters or more showed a higher percentage of tumor necrosis (cases 1 and 3) than those cases with a capsule thickness of 2 millimeters (cases 2 and 4).

Most of the operative findings of HCC and their relationship to the surrounding structures were adhesion of the tumor to the diaphragm and thickening of the hepatoduodenal ligament. The gross pathologic examination in case 2 showed a thin capsule of HCC about 2 millimeters in thickness with tumor mass protruding outside the capsule and extending to adhere to the diaphragm which also proved to be HCC from histologic examination, though the extension of the mass was not detected by the CT scan. (Fig. 3A to 3E).

DISCUSSION

Hepatocellular carcinoma is a highly lethal cancer. Surgical resection is the best management for cure, but is limited by the extent of the disease at the time of diagnosis, by the histologic type of tumor and by the high incidence of concurrent hepatic parenchymal disease, especially cirrhosis. For years, many articles regarding conversion of nonresectable to resectable hepatocellular carcinoma have been presented[10-12], but the procedures suggested were complicated and the complications from the treatment with hepatic arterial ligation plus hepatic arterial chemoinfusion plus radioimmunotherapy[10] may occur even more frequently.

The authors suggested a new regimen of treatment of gigantic hepatocellular carcinoma with patients in stage 2 disease (Okuda's)[9] which is considered to be an inoperable tumor by using transarterial oily chemoembolization recommended by Nakamura et al[8] and followed-up with serum AFP (as in cases 1 and 4) and CT scan of the upper abdomen (for all cases). Then wedge hepatic resection was performed using ultrasonic dissector which may be considered to be a safe operative procedure especially for HCC with cirrhosis (cases 1, 2 and 3), preserving the intrahepatic vasculatures which is an important factor for operating on a patient with a cirrhotic liver (Fig. 4).

Transcatheter oily chemoembolization is the preferred method of transarterial embolization in order to treat not only the main HCC, but also the daughter nodules[8] which may escape detection by CT scan as seen in case 2 (Fig. 3D).

We recommended the interval periods between last TOCE and wedge hepatic resection to be about 1 to 7 months (average 2.4 months) in order to decrease or get rid of the inflammatory edematous process which usually occurs after surgery and making the surgical procedure easier.

The serum AFP titer is an extremely useful tumor marker to indicate the result of treatment and for follow-up of the patients. It is an oncoprotein secreted from the endothelium of the yolk sac, hepatocyte of embryonic liver and feto-gastro intestinal tract. Usually the titer in the normal popula-

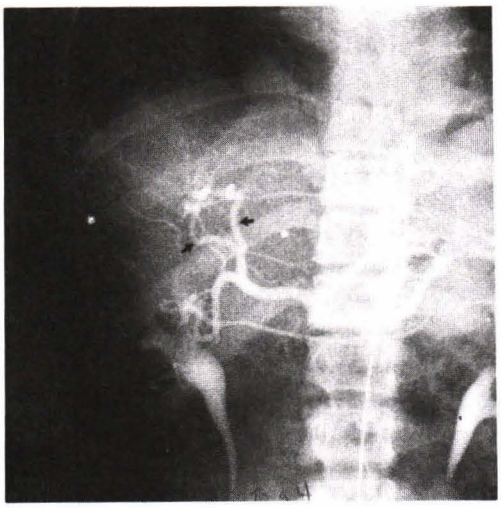


Fig. 4. Case 2 Fig. 3. Angiogram follow-up after wedge hepatic resection. Note : hepatic intravascular structure is well preserved by using ultrasonic dissector (arrow).

tion should not be above 20 ng/ml. It is a sensitive tumor marker, with decreased titer of serum AFP after TOCE or surgery as seen in Tables 2 and 3 indicating a good tumor response to treatment and with rising titer of serum AFP indicating recurrent HCC (Tables 2 and 3).

The reason for case 1 having a very long interval from last TOCE to wedge hepatic resection prior to surgery (7 months) was due to the fact that the serum AFP in this case had a very high titer from the initial examination prior to treatment (more than 20,000 ng/ml) and repeated TOCE had to be performed several times to lower the level of the serum AFP (Table 2) until the serum AFP reached 640 ng/ml with no residual tumor demonstrated by CT scan of the upper abdomen. It was then considered to be surgically resectable and was resected successfully without complication with a good surgical result at follow-up.

Table 4 shows a good relationship between tumor size after TOCE and thickness of tumor capsule to the percentage of tumor necrosis. A thick tumor capsule (cases 1 and 3) of 4 millimeters with a small tumor after TOCE showed 90 to 95 per cent tumor necrosis compared to case 2 and case 4 with bigger tumors left from the last TOCE and a thin capsule (2 millimeters) which showed only 80 per cent tumor necrosis. Our study is compatible to the work of Nakamura et al[13] and we can conclude that for complete or almost complete tumor necrosis after TOCE, the tumor should be small and thickly encapsulated and located at a site remote from collateral circulation also stated by Nakamura et al[13].

In the present study, no patient showed complete tumor necrosis after TOCE in the histologic examination of the surgical specimens and to accomplish a complete necrosis of HCC with no viable tumor cell, surgical resection was still indicated as mentioned by Yu YQ et al[16]. As shown in Table 2 (case 1), the serum (AFP) returned to zero after surgical resection which may indicate no viable tumor cell left after surgical resection.

The long-term follow-up showed a survival time which ranged from 48 months to 108 months which may be considered to be a satisfactory result of treatment.

In summary, the gigantic HCC can be converted from inoperable to operable by the combination of repeated TOCE and wedge resection of the tumor. Complete necrosis of the tumor with no viable tumor cell can not be achieved by TOCE alone, additional wedge surgical resection is indicated.

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การรักษามะเร็งตับชนิดปฐมภูมิด้วยการอุดตันหลอดเลือดตามหลังด้วยการผ่าตัด

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ได้รักษามะเร็งตับชนิดปฐมภูมิที่มีขนาดใหญ่ ๆ ในผู้ป่วย 4 ราย ซึ่งผ่าตัดไม่ได้เนื่องจากก้อนมะเร็งโตมาก สามารถทำการรักษาจนผ่าตัดได้โดยลดขนาดของมะเร็งด้วยการฉีดสารเคมีทำลายมะเร็ง เรียก ไมโตรไมซิน ซี ผสมกับลิพิโอดอล ซึ่งเป็นสารทึบรังสีตรวจหลอดน้ำเหลือง ผสมให้เข้าเป็นเนื้อเดียวกันแล้วฉีดเข้าหลอดเลือดของตับ และอุดตันหลอดเลือดของตับด้วยสารเจลโฟม (เป็นสารอุดตันหลอดเลือดชั่วคราว) แล้วติดตามผู้ป่วยจากคอมพิวเตอร์สแกนของตับและดูระดับแอลฟาฟีโตโปรตีนของเลือดซึ่งเป็นตัวดัชนีบอกการเกิดมะเร็งตับปฐมภูมิได้ดี เมื่อระดับแอลฟาฟีโตโปรตีนต่ำพอสมควรและประกอบกับจากคอมพิวเตอร์สแกนของตับหลังการรักษา พบว่าขนาดตับเล็กลงกว่าเดิมมากกว่าห้าสิบเปอร์เซ็นต์ ก็จะทำการผ่าตัดนำชิ้นเนื้อที่เป็นมะเร็งออก จากการทำการรักษาด้วยวิธีนี้ พบว่าผู้ป่วยสามารถมีชีวิตอยู่ได้นานอย่างต่ำสุดถึง 4 ปี มีผู้ป่วย 1 รายมีชีวิตอยู่ได้นานถึง 9 ปี จากการผ่าตัดมะเร็งตับเหล่านี้ พบว่ามีการตายของเนื้อเยื่อของมะเร็งจากการอุดตันหลอดเลือดด้วยสารเคมีดังที่กล่าวมาแล้ว ซึ่งการตายของเนื้อเยื่อเหล่านี้ยังขึ้นกับความหนาของถุงหุ้มของก้อนมะเร็ง ถ้ามีความหนาเกิน 4 มิลลิเมตร จะมีเปอร์เซ็นต์ของการตายของเนื้อเยื่อมากกว่าถุงหุ้มที่มีขนาดน้อยกว่า 4 มิลลิเมตร นอกจากนี้การตายของเนื้อเยื่อมะเร็งจากการอุดตันหลอดเลือดยังขึ้นกับขนาดของมะเร็งที่หดเล็กลงหลังการอุดตันหลอดเลือดหลาย ๆ ครั้ง ถ้ามะเร็งขนาดยิ่งเล็กยิ่งพบเปอร์เซ็นต์การตายของเนื้อเยื่อมีมาก ซึ่งแสดงว่าการรักษาได้ผลดี

จากการรักษามะเร็งตับดังกล่าวสามารถเปลี่ยนมะเร็งตับที่ผ่าตัดไม่ได้เป็นมะเร็งที่ผ่าตัดได้ ทำให้ผู้ป่วยมีชีวิตอยู่ได้ยาวนานดังตัวอย่างผู้ป่วยที่รักษาทั้ง 4 รายนี้

คำสำคัญ : มะเร็งตับ, การอุดตันหลอดเลือด, การผ่าตัด

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