Transcatheter arterial chemoembolization for superficial hepatocellular carcinoma induces adhesion

Seki S, Sakaguchi H, Hagihara A, Fujii H, Kobayashi S, Iwai S, Tamori A, Takeda T*

Department of Hepatology, Graduate School of Medicine, Osaka City University, Japan

Introduction

The therapies for hepatocellular carcinomas (HCCs) have remarkably developed during the recent one or two decades and the prognosis of HCC patients has subsequently much improved. At present we have been able to perform several therapeutic modalities for HCC, such as surgical resection, transplantation, loco-regional therapies including percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), and microwave coagulation therapy (MCT), chemotherapy, and transcatheter arterial embolization (TAE) and/or transcatheter arterial chemoembolization (TACE) [1]. According to the latest report of Liver Cancer Study Group of Japan during January 1, 2002 to December 31, 2003, 33.6% of 15,681 patients with HCC underwent surgical resection, 31.2% underwent loco-regional therapy, 29.6% underwent TAE/TACE, 4.9% underwent chemotherapy, and 0.8% underwent the other therapy [2]. As the report, TA(C)E is one of the most frequently performed modalities for HCC in Japan and has been validated effective in the treatment for advanced stages of HCCs. However, the efficacy of ordinary TAE/TACE has not been able to expect complete response of the targeted HCC nodules. The rate of complete response of TAE/TACE was 27.8%, and the 5-year survival rate was 22.6%. These results of TAE/TACE seemed to be lower in comparison to those of loco-regional therapies including PEI, MCT, and RFA, whose complete response was 82.2% and 5-year survival 42%. In these situations, we have experienced membranous adhesions between superficial position of HCC nodules and peritoneum and/or omentum in some patients with these HCCs nodules treated with TAE/TACE prior to the laparoscopic loco-regional treatments for these nodules performed at our hospitals in order to achieve complete response [3]. With respect to the adhesion, we would like to consider the positive or negative efficacy of TAE/TACE for these HCC nodules and the usefulness of laparoscopic thermal ablation for these HCC nodules.

* CORRESPONDING AUTHOR:
Health Welfare Center of Osaka Abeno Ward
1-1-40 Huminosato
Abeno-ku, Osaka 548-8501, Japan
Tel: +81-6-6622-9861; Fax: +81-6-6629-1349
e-mail: sh-seki@city.osaka.lg.jp (Shuichi Seki)

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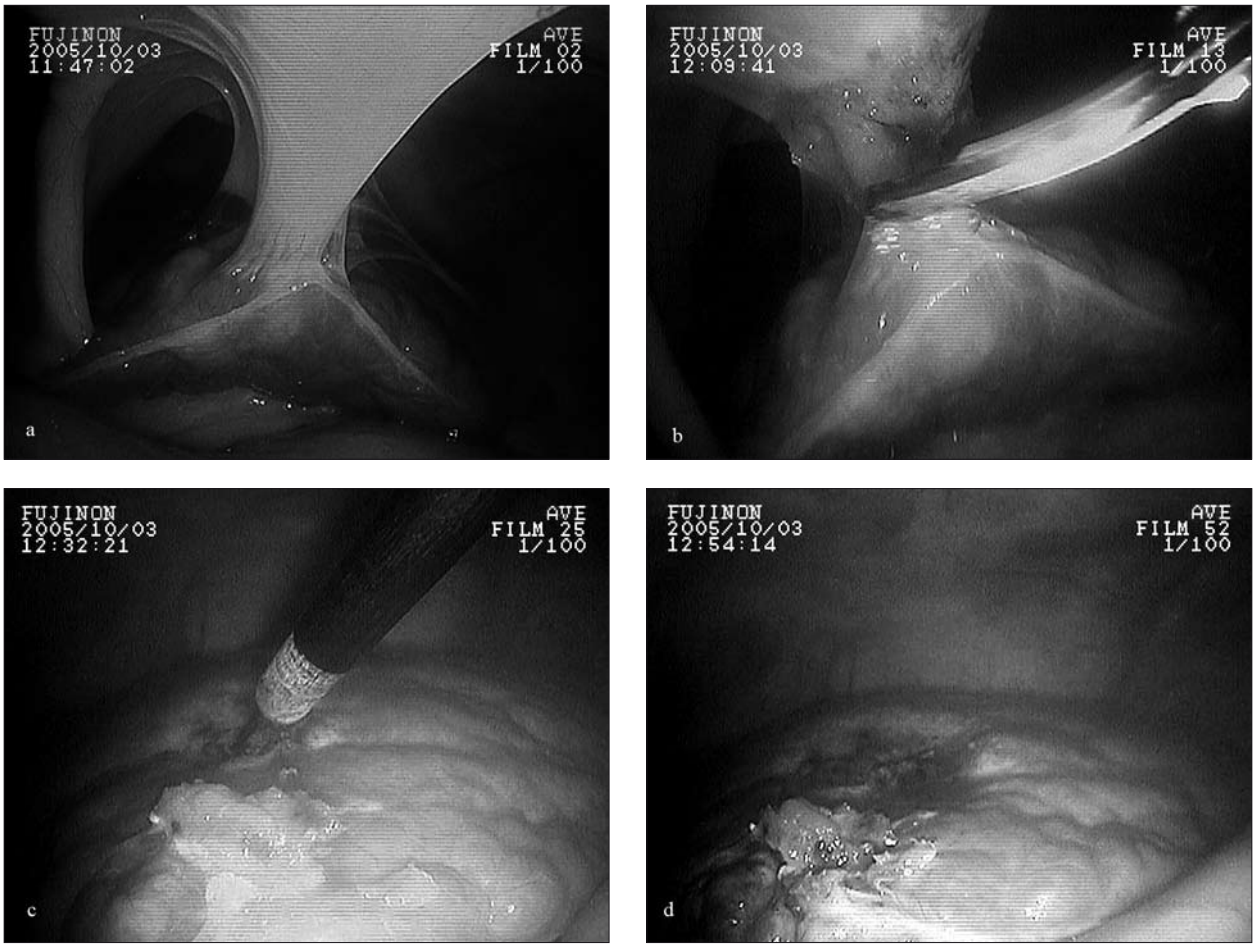
Patients and methods

During April 1, 1995 to October 31, 2005, we performed laparoscopic thermal ablation (LTA), MCT or RFA, for 119 consecutive patients with superficial position of HCC nodules at our hospital. Eighty-eight of the 119 patients (73.9%) underwent the LTA for their primary HCC nodules, and the remaining 31 (26.1%) underwent LTA for their secondary or tertiary HCC nodules. At laparoscopy, we found the adhesion between superficial HCC nodule and peritoneum and/or omentum in seven patients of the 119 (5.9%) patients. We analyzed the correlation between adhesion and history of the treatments performed prior to LTA in the 7 patients. Demographic and clinical data on the 119 patients who underwent LTA were summarized in *Tab. 1*. The 119 patients consisted of 72 males and 47 females. Mean age of the 119 patients was 66 yr (range 46-87). With regard to Child-Pugh classification, 79 were classified into class A, 39 in class B, and 1 in class C, respectively. The causative agent of chronic liver disease in the 119 patients was hepatitis C virus in 110, hepatitis B virus in 3, alcohol in 4, Wilson disease in one, and primary biliary cirrhosis in one. The mean diameter of HCC was 18.8 (minor axis) x 20.6 (major axis) mm (SD 6.0 x 6.6 mm). Histological examinations by fine needle biopsy were performed in 37 patients. Well differentiated HCC was diagnosed in 21 patients, moderately differentiated HCC in 14, and poorly differentiated HCC in 2. Alpha-fetoprotein was measured in 91 patients.

Figure 1. **Laparoscopic microwave coagulation. a. Adhesion between superficial HCC nodules and peritoneum. b. Adhesions are cut with harmonic scalpel. c. Superficial HCC nodules are treated with MCT. d. Coagulation necrosis forms decompression with LMCT**



Statistical analysis

Categorical variables were compared statistically using the chi-squared or Fisher's exact test where appropriate. Continuous variables were compared using the Wilcoxon rank sum test. The correlation between continuous variables was tested using Spearman correlation coefficients. Multivariate analysis was performed using logistic regression analysis. All statistic analyses were performed using the Statistic Analysis System (SAS Institute Inc.). P values of less than 0.05 were considered significant.

Results

At laparoscopy, we found adhesion between superficial HCC nodules treated previously and peritoneum and/or omentum in 7 patients. Of the 7 patients, one underwent treatment with LTA for the primary HCC after TAE performed at other hospital about one month prior to admission to our institution. The other 6 patients were treated for local progression tumor of the secondary or tertiary HCC on the liver surface after the initial therapy at our institution (*Fig. 1*). We cut the adhesion with harmonic scalpel and treated HCC with MCT or RFA. Some adhesion tissues contained vessels. Demographic and clinical data on the 7 patients were summarized in *Tab. 2*. They consisted of three men and four women. Superficial HCC nodule

Table 1. **Baseline data on 119 patients treated for superficial hepatocellular carcinoma nodules**

Men/women	**72/47**
Initial/second laparoscopic therapy	88/31
Mean age, years	66 (range 46-87)
Child-Pugh classification	
A /B/C	79/39/1
Cause of liver disease	
HCV/HBV/Alcohol/Wilson/PBC	110/3/4/1/1
Diameter of HCC (mm)	18.8 x 20.6 (SD 6.0 x 6.6)
Histological findings for HCC (n=37)	
Well/Moderately/Poorly	21/14/2
Alph-fetoprotein (ng/ml) (n=91)	
0-20/21-200/201<	44/36/11

HCV – hepatitis C virus; HBV – hepatitis B virus; PBC – primary biliary cirrhosis; HCC – hepatocellular carcinoma; SD – standard deviation

***Table 2*. Baseline data on the 7 patients with adhesion between HCC and peritonium and/or omentum**

	Age/Sex	Location/size of HCC	Previous therapy	Primary or local progression
1	72/M	S3/14 x 17 mm	TAE	primary
2	57/M	S3/23 x 25	TAE + PEI	local progression
3	75/F	S3/13 x 21	TAE + PEI	local progression
4	77/F	S3/28 x 28	TAI	local progression
5	73/M	S6/24 x 26	TAE	local progression
6	61/F	S6/30 x 30	TAE + PEI	local progression
7	81/F	S3/16 x 17	TAE	local progression
		S3/17x 18		

HCC – hepatocellular carcinoma; M – male; S – subsegment; TAE – transcatheter arterial embolization; PEI – percutaneous ethanol injection; F – female; TAI – transcatheter arterial infusion

***Table 3*. Data on 25 patients without adhesion who underwent LLRT for secondary or tertiary HCC**

Men/women	14/11
Mean age years (range)	67 (51-82)
Child-Pugh, number A/B/C	14/10/1
Cause of liver disease	
HCV/HBV/Alcohol	23/2/0
Diameter of HCC, minor x major (mm)	20.5 x 20.6 (SD 7.0 x 7.4)
Histology of HCC (differentiation)	
Well/moderately/poorly (n=5)	1/3/1
Alpha-fetoprotein (ng/ml)	
0-20/21-200/201< (n=23)	8/11/3
Previous therapy (consecutive)	
PEI/TAE/TAE +PEI/MCT/RFA/TAE;RFA	12/10/7/5/2/1

LLRT – laparoscopic loco-regional therapy; HCC – hepatocellular carcinoma; HCV – hepatitis C virus; HBV – hepatitis B virus; PEI – percutaneous ethanol injection; TAE – transcatheter arterial embolization; MCT – microwave coagulation; RFA – radiofrequency ablation

with adhesion was located in subsegment 3 in 5 patients and in subsegment 6 in two. The diameter of HCC ranged from 13 to 30 mm. All seven patients previously underwent TAE, TAI, or combination of TAE and PEI for the superficial HCC as the therapy (*Fig. 2*). After the therapy with TAE, TAI, or TAE + PEI for the primary, secondary, or tertiary HCC, local progression tumor developed in the 7 patients. We completely treated these local progression tumors with LTA.

Next, we examined 25 patients without adhesion, who were treated for secondary or tertiary HCC with LTA (*Tab. 3*). The 25 patients consisted of 14 men and 11 women. The mean age was 67 years (range 51-82 years). With respect to Child-Pugh classification, 14 patients were classified into class A, 10 in class B, and one in class C. Most of patients contracted cirrhosis with HCV infection. The mean diameter of HCV was 20.5 mm (minor axis) x 20.6 mm (major axis) (SD 7.0 x 7.4 mm). Diverse therapies were previously performed for HCCs which were located in comparatively deep positions of the liver or dorsal subsegments. Twelve patients were treated with PEI, 10 with TAE, 7 with TAE + PEI, 5 with MCT, 2 with RFA, and one with TAE + RFA. In this study, PEI and TAE dominated in several forms of therapies, but we could not find any adhesion in these patients by laparoscopy. Therefore, TAE and PEI for HCCs in deep positions or dorsal subsegments might not induce adhesion.

In statistical analysis, any variables, such as sex, age, causes of chronic liver disease, primary or secondary treatment, and Child-Pugh classification, were not significant (data not shown). There is the history of TACE for the superficial HCC nodule as a different factor between the superficial HCC patients with and without adhesion.

Discussion

In current years, selection range of therapeutic modalities for hepatocellular carcinoma has much expanded. Generally speaking, in many countries, in particular Japan, physicians perform loco-regional therapies including PEI, MCT, and RFA, radiologists perform transcatheter arterial chemo-embolization (TACE) including transcatheter arterial infusion (TAI) and radiation, and surgeons perform hepatic resection and transplantation. With the improvement in skills and implements of therapeutic modalities, some suggested algorithms of therapies for HCC have become available [1,4]. As curative treatments, hepatic resection, liver transplantation, PEI, and RFA have been selected [1,5-8], but TAE has been selected for HCCs at relatively progressed stages [9-12]. However, among these therapeutic modalities for the advanced HCCs, TAE including TACE and TAI dominated in Japan [2].

We have performed laparoscopic loco-regional therapy for superficial position of HCC nodule and the therapeutic efficacy and complications of LTA have been reported in recent years [3]. In these situations, we found adhesions between the treated HCC and peritoneum and/or omentum containing vessels. As

Figure 2. **Radiological study and intervention. a. Computed tomographic hepatic arteriography reveals positive staining of HCC nodule in subsegment 3. b. Positive staining of HCC nodules (arrows) is visible. TACE was performed. c. Local progression is found about one year after TACE. d. Complete response is confirmed after LMCT for local progression of HCC**

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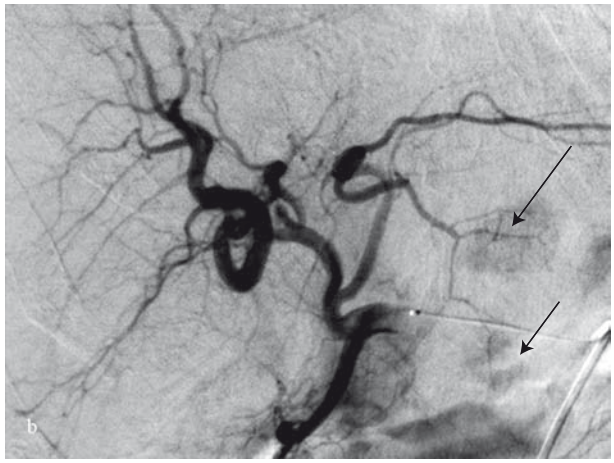

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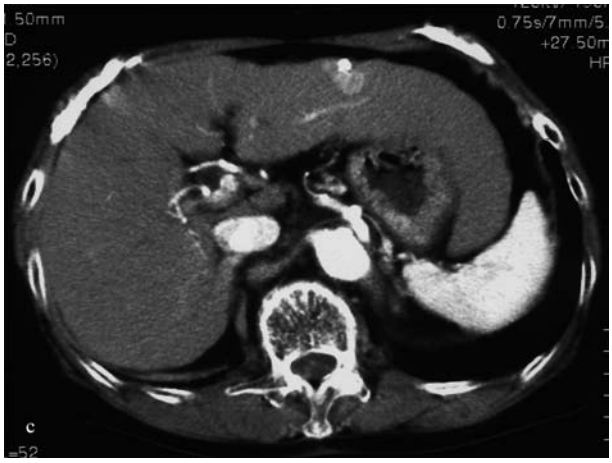

shown *Tab. 2*, all 7 patients with adhesion had histories of treatments with TAE for the superficial HCC. On the other hand, all 25 patients had the histories of treatments with diverse modalities including TAE and PEI for the HCCs in deep positions of the liver or dorsal subsegments had no adhesions. Taken together, therefore, TAE for superficial HCC might induce adhesions between the treated HCCs and other tissues including vessels. The rates of complete response of TAE for HCC have been reported, 50%, 63.3%, and 23.5%, respectively [5-7]. It is very difficult for TAE alone to achieve complete response for superficial HCC, so we should add the other therapeutic modalities, PEI, MCT, or RFA when we hope complete response. Rather than the additional therapy, avoidance of TAE for the superficial HCC may be preferential in the treatments when we expect curative treatments. In any case, we could completely treat the adhered HCC nodules with laparoscopic MCT or RFA, in addition to laparoscopic resection [13]. Therefore, we would like to emphasize that LMCT or LRFA is very useful for the superficial HCCs, if they had adhesion.

In conclusions, we have experienced 7 patients with adhesions between the treated superficial HCCs and omentum and/or peritoneum including vessels, who had histories of TAE for these HCCs. Therefore, we should avoid the treatment with TAE alone for superficial HCC when we hope to achieve complete response as a primary curative treatment. However, LMCT and LRFA are useful therapeutic procedures for the superficial HCC nodules, even if HCC nodules have adhesions.

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