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A Prospective Randomized Trial of the Preventive Effect of Pre-operative Transcatheter Arterial Embolization against Recurrence of Hepatocellular Carcinoma

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To clarify whether pre-operative transcatheter arterial embolization (TAE) improves survival after hepatectomy, a prospective randomized comparative study was done. Of a total of 115 registered patients having solitary hepatocellular carcinoma (HCC) 2 to 5 cm in diameter, 18 (15.7%) were excluded after randomization. As a result, 97 patients were chosen as subjects and divided into two groups: hepatectomy with (group A: n=50) and without (group B: n=47) pre-operative TAE. The period of observation of the patients who survived the surgery was between 4.0 and 6.6 years. The randomization appeared to have provided well-balanced groups of patients and the clinico-pathological characteristics of the two groups were quite similar. The necrotic part of the cancerous lesions, as confirmed by operative specimens, amounted to 74.8±33.4% (mean±SD) in group A and 6.8±7.2% in group B ($P<0.01$). However, the cancer-free survival rates after hepatectomy in both groups showed little difference (39.1±7.0 (%±SE) and 31.1±0.1, respectively). We speculate that TAE is not effective against such HCC accessory lesions as minute intrahepatic metastasis and tumor thrombus and that pre-operative TAE does not improve post-operative survival.

Key words: Pre-operative TAE — Hepatocellular carcinoma — Recurrence — Survival rate

In the late 1970's, transcatheter arterial embolization (TAE) was introduced for the treatment of hepatocellular carcinoma (HCC). Initially it was used for the treatment of unresectable HCC.[1–4] We found that the results achieved by using TAE for unresectable HCC were much better than those obtained by other non-surgical treatments such as systemic or regional chemotherapy.[5,6] Many surgeons have used TAE as a pre-operative adjuvant therapy for HCC, expecting that TAE may improve post-operative long-term survival. A few studies have compared the long-term results after hepatectomy for HCC between patients with or without pre-operative TAE.[7–10] While some studies have supported the use of pre-operative TAE, others have not. In none of these studies were the patients randomized and compared with historical controls. Furthermore, the methods and the materials used for TAE were not uniform. Whether pre-operative TAE for HCC is effective in improving post-operative long-term survival or not, is still controversial.

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A study group was organized to test the effect of pre-operative TAE against HCC recurrence using a prospective randomized method. We report here the results of this prospective randomized study.

MATERIALS AND METHODS

In 1987, the Ministry of Health and Welfare established a study group (62-3, Chairman: Hiroshi Hasegawa) for prospective randomized trials to test the effects of pre-operative TAE. Nineteen leading institutes conducting HCC treatment in Japan joined this multi-institutional study. Between July 1987 and December 1989, this group collected and registered cases. Follow-up of the cases and data analyses were then transferred to successive hepatic surgery study groups (3-38 & 5-25, Chairman: Susumu Yamasaki).

Eligibility of the patients

Host-related factors: Male patients 65 years old or younger with untreated non-recurrent HCC were eligible for the study. Patients having a double primary malignancy or a history of other malignancy were excluded.

Function-related factors: Patients without severe liver cirrhosis, having a value of 40% or less for Indocyanine Green 15 minutes' retention rate (ICG-R15) and serum total bilirubin of 1.5 mg/ml or less prior to embolization, in addition to absence of cardiovascular, renal and/or cerebro-neural complications were eligible.

Cancer-related factors: Only patients with HCC, diagnosed by imaging diagnostic modalities, having tumors from 2 to 5 cm in diameter and having a single nodule or a single nodule with satellite nodule(s) which could be removed *en bloc* were eligible. Pre-operative confirmation of histological diagnosis was not required.

Methods of embolization and hepatectomy

Hepatic arterial embolization: A catheter was inserted selectively into the proper, right or left hepatic artery by Seldinger's method. Twenty mg of doxorubicin (Adriamycin, ADM) was dissolved in 2.5 ml of iodized watery contrast medium (Urografin) and mixed with 5 ml of iodized oil contrast (Lipiodol). When the catheter was inserted into the proper position in the hepatic artery, the above solution was injected and was followed by another injection of 1 to 3 mm gelatin sponge cubes soaked in Urografin. The determination of the extent of the liver to be embolized was left to each individual institute.

Hepatectomy: The operative procedure for each patient was left to each institute.

Prospective randomization Patients were randomized using the envelope method: group A with pre-operative TAE, group B without TAE.

Measurement of the necrotic area and tumor size As an indicator of tumor necrosis, the area of necrosis and changes in the tumor size were measured. Although ideally the necrotic area should be expressed as the volume of the necrotic tumor tissue (cm^3), measurement of the volume is not easy. We measured the percent necrosis on several cross sections of operative specimens. Tumor size was also measured pre-operatively by imaging techniques. Post-operatively, the longest diameter on the largest cross-section of the tumor was measured and was regarded as the diameter of the tumor.

RESULTS

Registration and follow-up Between September 1987 and December 1989, 115 cases in total were registered in the 19 institutes; 57 cases were assigned to group A and 58 to group B. Seven cases from group A and 11 cases from group B were later excluded for the reasons summarized in Table I. The final number of subjects chosen for evaluation of cancer-free survival after hepatectomy was 97 patients: 50 in group A and 47 in group B. They were followed up until June 1994. The longest and shortest intervals between the date of hepatectomy and the last follow-up of surviving patients were 6.63 years and 4.03 years, respectively. The mean value of the follow-up interval was 5.55 years and the median value was 5.66 years.

Patients' characteristics The clinico-pathological background of the randomized patients in the two groups are summarized in Table II. Both the distribution of patients and their clinico-pathological characteristics were similar between the two groups. The only difference between the two groups was in tumor size as measured on the operative specimens.

Short-term results In one patient in group A, deterioration of liver function was observed after pre-operative TAE, and hepatectomy was therefore not done. In group B, two patients also exhibited deterioration after hepatic angiography, and hepatectomy was also not performed. The rates of surgery-related mortality, death within 30 days following surgery and hospital death, were 5.7% (3/53) in group A and 7.8% (4/51) in group B, with no significant difference between the two groups.

Table I. Reasons for Subject Exclusion

Reason for exclusion	Group A	Group B
Deterioration of hepatic function after entry	1	2
TAE impossible due to injury of the intima of the hepatic artery	1	—
Illegitimate injection of ADM at TAE	—	1
Surgery-related mortality	3	4

Table II. Clinico-pathological Characteristics of the 2 Groups

	Group A	Group B	Difference
Host-related factors			
Age (Mean±SD)	54.9±6.4	57.1±4.9	n.s.
ICG-R15 (%, Mean±SD)	18.1±8.6	15.9±8.5	n.s.
T. Bil (mg/dl, Mean±SD)	0.76±0.29	0.79±0.28	n.s.
Cancer-related factors			
Tumor size (on imaging, cm, Mean±SD)	3.1±0.8	3.3±0.9	n.s.
Tumor size (on specimen, cm, Mean±SD)	2.6±0.9	3.2±0.9	$P<0.01$
Vp (+)[a] incidence (on imaging)	0/50	1/46	n.s.
Vp (+)[a] incidence (on specimen)	1/49	3/44	n.s.
Edmondson's histologic grade 1:2:3	5:21:9	3:29:14	n.s.
Macroscopic type A: B: C: D: E: F[b]	34:8:3:1:2:2	32:6:6:1:1:1	n.s.
Treatment-related factors			
Embolized area 1:2:3:4[c]	15:30:4:1	—	
Resected area 1:2:3:4[d]	20:16:13:1	24:7:13:3	n.s.
Specimen weight (g, Mean±SD)	152.3±122.7	186.6±159.5	n.s.
TW[e] (mm, Mean±SD)	9.7±8.8	9.0±8.8	n.s.

a) Abbreviation of macroscopic (Vp) and microscopic (vp) portal vein invasion defined by the General Rule of Primary Liver Cancer of Study Group of Liver Cancer of Japan.
b) Macroscopic types of HCC defined by the General Rule of Primary Liver Cancer of Study Group of Liver Cancer of Japan. A, solitary nodular; B, solitary nodular with perinodular proliferation; C, multinodular fuged; D, multinodular; E, massive; F, unknown.
c) 1, whole liver; 2, lobular; 3, segmental; 4, unknown.
d) 1, limited resection; 2, subsegmentectomy; 3, segmentectomy; 4, lobectomy.
e) The smallest distance between tumor edge and surgical stump.

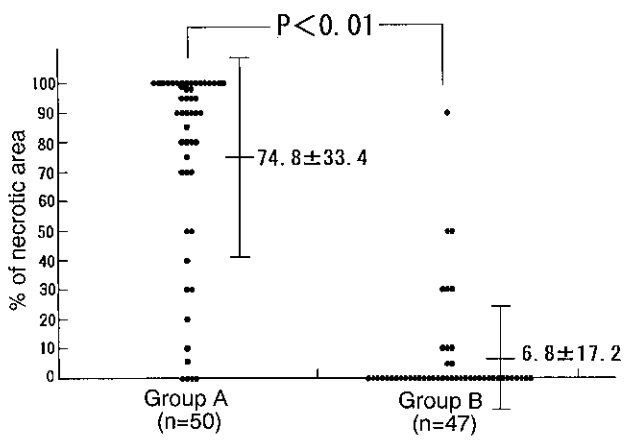

Fig. 1. Rate of cancer necrosis. Rates of necrosis in cancer tissue observed in the operative specimens were compared between groups A and B. The mean values of the two groups were markedly different ($P<0.01$).

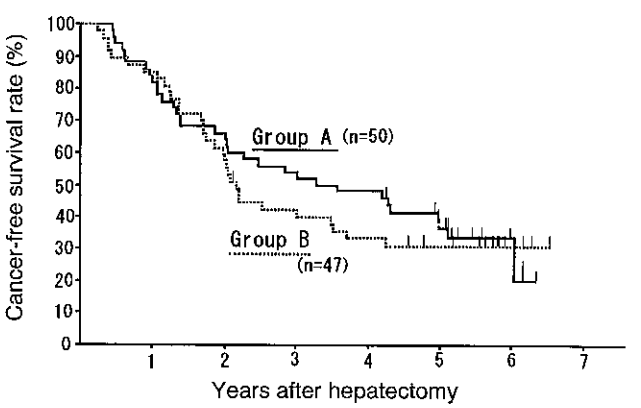

Fig. 2. Cancer-free survival rates after hepatectomy. The cancer-free survival rates after hepatectomy of the two groups were compared. There was no significant difference between the groups according to the generalized Wilcoxon's test.

The direct effects of pre-operative TAE on tumors The percent necrotic area of the tumors was evaluated using resected specimens. The mean±SD (%) of the percent necrosis was 74.8±33.4% in group A and 6.8±17.2% in group B (Fig. 1). This difference was significant ($P<0.01$). Changes in the longest diameter of the tumors measured pre-operatively by imaging techniques and post-operatively using operative specimens were −0.57 ±0.82 cm (mean±SD) in group A and −0.22±0.58 in group B ($P<0.05$).

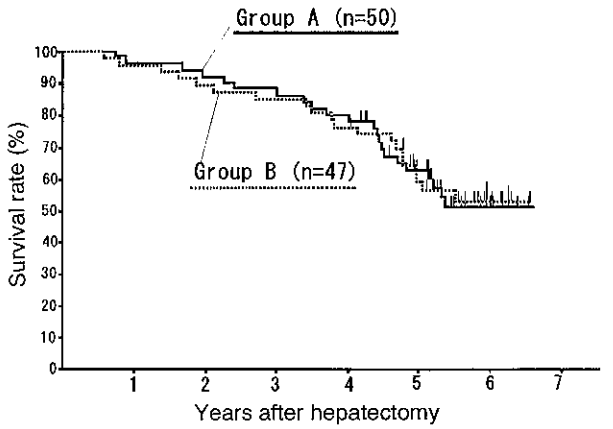

Fig. 3. Survival rates after hepatectomy. The survival rates after hepatectomy of the two groups were compared. There was no significant difference between the groups according to the generalized Wilcoxon's test.

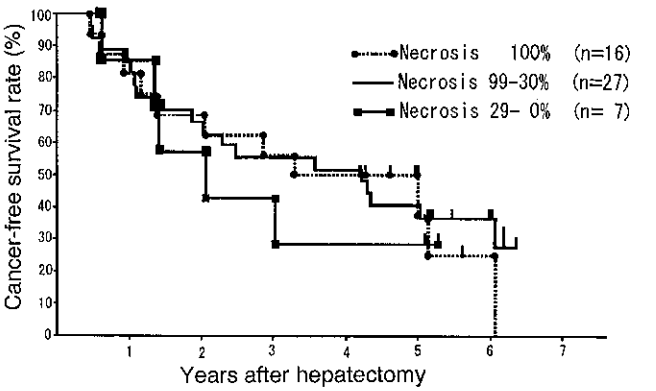

Fig. 4. Cancer-free survival rates according to the degree of tumor necrosis. The cancer-free survival rates after hepatectomy were compared among the three subgroups in group A who had been treated with pre-operative TAE. The subgroups were classified according to the degree of tumor necrosis observed on the resected specimens. There was no significant difference between the groups according to the generalized Wilcoxon's test.

Effects of pre-operative TAE on long-term results On June 30, 1994, the 5-year cancer-free survival rates (%±SE) after hepatectomy in group A (n=50) and group B (n=47) were 39.1±7.0 and 31.1±0.07, respectively. The 5-year survival rates of the two groups were 62.7±0.07 and 61.7±0.07, respectively. The differences between the cancer-free survival rates and between the survival rates of the two groups were not significant according to the generalized Wilcoxon's test. Curves showing the cancer-free survival and survival rates are shown in Fig. 2 (cancer-free survival) and Fig. 3 (survival).

Long-term results according to the degree of tumor necrosis In group A, cancer-free survival rates were compared among the three groups according to the degree of tumor necrosis; 100% necrosis (n=16), 99–30% necrosis (n=27) and less than 30% necrosis (n=7). The 5-year cancer-free survival rates (%±SE) of these three groups were 37.5±14.3%, 36.7±9.4% and 28.6±17.1%, respectively (Fig. 4). The differences were not significant.

DISCUSSION

When TAE was introduced for the treatment of HCC, many clinicians felt it to be superior to other non-surgical treatments and to have a beneficial effect on HCC. Good survival rates following TAE have been reported. However most studies on the long-term results of using TAE were non-randomized. Only a few studies have examined the effects of TAE on long-term survival using prospective randomized tests of patients having unresectable HCC. Although Lin *et al.*[11] reported positive effects of TAE on long-term survival, Pelletier *et al.*[12] did not support the use of TAE for the treatment of HCC. The difference in the conclusions of the two randomized studies may have arisen from differences in the functional backgrounds of the patients. In Pelletier's study, 71% of patients who received TAE were in stages 2 or 3 according to Okuda's classification,[13] while the patients reported in Lin's study seemed to have had much better liver function. TAE is more or less hepatotoxic. In patients with more than 2 mg/dl of total bilirubin, the use of TAE is rather risky and when the total bilirubin is more than 3 mg, TAE is contraindicated.[14] This means that suitable candidates for TAE are those patients who are in the better part of stage 1 according to Okuda's classification. The two above-mentioned studies showed that TAE has a beneficial effect on patient with inoperable HCC who have good liver function, but not on those with poor liver function. Regarding the anatomical status of the HCC in both papers, the descriptions given were too scanty to allow evaluation of this factor as a possible cause of the difference in outcome.

The present study examined the effect of pre-operative TAE on HCC recurrence using a prospective and randomized method. The livers of patients in this study were resectable both anatomically and functionally and their liver functions were in the better part of stage 1 according to Okuda's classification.

In this study, the direct effect of TAE on gross HCC lesions was confirmed. We found that although the percent necrotic area in specimens taken from patients treated by pre-operative TAE was much higher than in those not treated pre-operatively, there were no significant differences in survival after hepatectomy.

At the beginning of the 1980's, the direct effect of TAE on pre-operatively embolized HCC specimens obtained by hepatectomy was reported by Hasegawa *et al.*[15, 16] They noted a high incidence of necrosis induced by TAE in the main tumor. Complete necrosis was found in 27% of the cases, and partial necrosis (more than 50% of the area) in 72% of the cases. However, the complete or partial necrosis induced by TAE in the daughter nodules (i.e. intrahepatic metastatic lesions which had been recognized macroscopically) was noted in only 40% of the cases. The effect of TAE on microscopic tumor thrombi in the portal vein was not analyzed. Since the detection rates of these microscopic thrombi differed so greatly among member institutes, the necrotic effects induced by TAE could not be compared. It should be noted that microscopic intrahepatic metastasis, including tumor thrombus in the portal vein, frequently occurs.[17] The direct effect of TAE on HCC accessory lesions is unsatisfactory. Sakurai *et al.*[18] reported that 4 of 14 patients had daughter nodules, all of which were viable after TAE. Hwang *et al.*[19] noted the presence of intact tumor cells after TAE in 4 out of 5 cases which had daughter nodules. As the percent necrosis in the daughter nodule induced by TAE is much lower than that in the main tumor, microscopic tumor thrombus is suspected to be resistant to TAE. Thus, according to short-term studies done after hepatectomy, it is strongly suspected that the cause of HCC recurrence is residual minute lesions. The results in the present study are compatible with this suggestion.

Adachi *et al.*[10] reported no difference between disease-free survival rates in patients with or without pre-operative TAE. However, they noted that the disease-free survival rates of patients with incomplete tumor necrosis who were treated by pre-operative TAE were lower than in those who had had complete necrosis, or in those without TAE necrosis, and or even in those without pre-operative TAE. They speculated that in cases of partial necrosis, the remaining viable tumor cells are less firmly attached, and thus are more likely to be dislodged into the bloodstream and also that viable tumor cells metastasize during hepatic resection due to surgical manipulation. They also hypothesized that the major cause of HCC recurrence was the metastasis of the cancer cells due to surgical manipulation. Their study showed that out of 10 patients with complete necrosis induced by pre-operative TAE, 6 had recurrences within 5 years. These findings suggest that the cause of HCC recurrence is not the metastasis of cancer cells released during surgical manipulation, but rather occult intrahepatic metastasis before surgery or HCC multicentricity. Our present study found no differences among the survival and cancer-free survival rates of patients who received pre-operative TAE according to the degree of tumor necrosis (Fig. 4). Our results suggest that long-term survival rates after hepatectomy do not depend on the degree of tumor necrosis in patients who undergo preoperative TAE, and surgical manipulation is not the main cause of HCC recurrence.

We therefore, conclude that the use of pre-operative TAE does not improve the post-operative prognosis for HCC patients, since the direct effect of TAE on accessory HCC lesions is unsatisfactory.

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