

Five-year survival after transcatheter chemoembolization for hepatocellular carcinoma

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Abstract. The 5-year cumulative survival rate of 443 patients who underwent transcatheter chemoembolization (TCE) for non-resectable hepatocellular carcinoma (HCC) before December 1986 was 8.0%, and 29 patients survived for 5 years or more. Of these 29 patients, 25 were men and 4 were women; their mean age was 63.9 years. Macroscopic classification showed lesions of the single nodular type in 16 cases, the multiple nodular type in 10 cases, and the massive type in 3 cases; 12 of the single nodular lesions measured 5 cm or less in size. The TNM classification showed lesions of stage I in 3 cases, stage II in 14 cases, stage III in 6 cases, and stage IV in 6 cases. Lesions classified as Child A were found in 23 patients, and they were thus much more common than Child B lesions (2 patients) and Child C lesions (1 patient). The response was analyzed in relation to the use of iodized oil (Lipiodol). It was used in 215 of the patients, and the 5-year cumulative survival rate of those patients was 12.9% (23 of them survived for 5 years or more). Lipiodol was not used in 228 patients, and they showed a 5-year cumulative survival rate of 3.4%, with 6 patients surviving for 5 years or more. The 6 patients with stage III disease and the 6 with stage IV disease received Lipiodol. TCE with Lipiodol thus contributed greatly in prolonging the survival of patients with HCC complicated by intrahepatic metastases or intraportal tumor thrombi.

Introduction

Hepatocellular carcinoma (HCC) has a very poor prognosis. One reason is that there is little chance of success with hepatic resection of this carcinoma because liver cirrhosis is often present [2, 12, 13]. Transcatheter arterial embolization [1, 6, 14, 18, 19], which was introduced toward the end of the 1970s, has attracted much attention as a treatment for HCC because of the earlier poor prognosis.

Embolization or chemoembolization has been used for more than 10 years, and the response to this therapy improved after the introduction of iodized oil (Lipiodol; Laboratoire Guerbert, France) [5, 9, 10, 15, 17, 20]. However, the long-term survival following this treatment has not yet been fully assessed. The only report on 5-year survival following embolization was presented by Ikeda et al. [4].

We first calculated the accurate 5-year cumulative survival rate for patients who had undergone transcatheter chemoembolization (TCE) more than 5 years earlier, and then the data on 29 patients who survived for 5 years or more were analyzed. Survival was also analyzed in relation to the use of Lipiodol, and the results were interesting, as described below.

Materials and methods

Patients. A total of 443 patients with HCC who underwent TCE in Osaka University Hospital and its affiliated hospitals between November 1979 and December 1986 were selected for the study. The diagnosis of HCC was established by ultrasonography, CT, angiography, and determination of the α -fetoprotein (AFP) level. All 29 patients who survived for 5 years or more after TCE also had liver cirrhosis, and they showed clear-cut tumor stains on hepatic angiograms, a rise in AFP levels to 1,000 ng/ml or more, or tumor growth before treatment with TCE.

TCE was contraindicated in cases with complete occlusion of the main trunk of the portal vein. Incomplete or locoregional TCE was used in patients with impaired hepatic function (total bilirubin, 2.0 mg/dl or more). Patients who underwent hepatectomy following TCE were excluded from the study.

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Precis: Analysis of the five-year survival of 443 patients receiving transcatheter chemoembolization for HCC showed that TCE prolonged life, and concomitant use of lipiodol improved the results.

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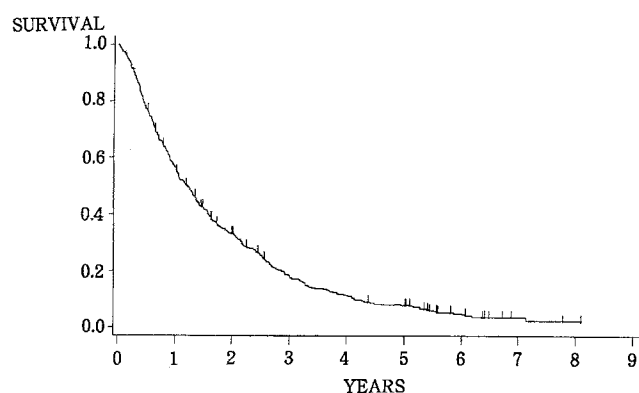


Fig. 1. Cumulative survival curve after TCE for HCC ($n = 443$; Kaplan-Meier method)

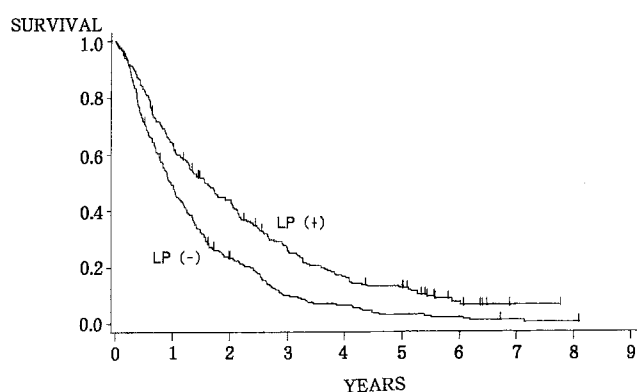


Fig. 2. Cumulative survival curves comparing the Lipiodol group [LP(+), $n = 215$] with the non-Lipiodol group [LP(-), $n = 228$] ($P = 0.0001$, log-rank test)

Procedures. All patients received gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, USA) together with an anticancer drug by injection into the proper hepatic artery or into its distal branches. Even if the catheter could be advanced only up to the common hepatic artery, the injection was made after the balloon catheter had been inflated at that point [7].

Many patients received 40–80 mg of doxorubicin hydrochloride (Adriacin; Kyowa Hakko Co., Ltd., Tokyo, Japan). The mean dose given the patients who survived for 5 years or more was 53.6 mg. Patients who also had heart disease were given 10–20 mg of mitomycin C (Mitomycin Kyowa-S; Kyowa Hakko Co., Ltd., Tokyo, Japan) or 100 mg of cisplatin (Randa; Nihon Kayaku Co., Ltd., Tokyo, Japan).

After 1983, a mixture of Lipiodol with an anticancer drug was injected before the dose of gelatin sponge. The Lipiodol dose was 3–10 ml in most patients, and the mean dose given the patients who survived for 5 years or more was 5.5 ml. TCE was repeated in many patients at intervals of 6–12 months. The patients who survived for 5 years or more had undergone 1–6 courses of TCE (mean, 3.3 courses).

Results

Cumulative survival rate

Figure 1 shows the survival curve for the 443 patients, which was calculated by Kaplan-Meier's method. The cumulative survival rate was 56.3% for 1 year, 33.3% for

Table 1. TNM stages of the 29 5-year survivors

Stage I	3	(Solitary, ≤ 2 cm, without vascular invasion)
Stage II	14	(13: Solitary, >2 cm, without vascular invasion 1: Multiple, one lobe, ≤ 2 cm, without vascular invasion)
Stage III	6	(1: Solitary, >2 cm, Invasion of a second branch of portal vein 5: Multiple, one lobe, >2 cm)
Stage IV	6	(4: Multiple, >1 lobe 1: Invasion of a first branch of portal vein 1: Invasion of a first branch of portal vein and a hepatic vein)

Table 2. Relationship between the disease stage^a and the two groups (Lipiodol or non-Lipiodol)

Stage	I	II	III	IV	Total
Lipiodol group	2	9	6	6	23
Non-Lipiodol group	1	5	0	0	6

^a According to the TNM classification

2 years, 18.3% for 3 years, 11.8% for 4 years, and 8.0% for 5 years. The rate was also determined separately for 228 patients who did not receive Lipiodol and 215 patients who did receive it. Figure 2 shows the survival curves for these two groups of patients, indicating that the survival rate improved markedly in the patients who also received Lipiodol (log-rank test, $P = 0.0001$). The 5-year cumulative survival rate was 3.4% before the use of Lipiodol and 12.9% after its introduction.

Patients who survived for 5 years or more

A total of 29 patients, including 25 men and 4 women, survived for 5 years or more after TCE. They were 43–79 years old (mean age 63.9 years). In all, 2 were in their 40s, 12 were in their 50s, 7 were in their 60s, and 8 were in their 70s. The macroscopic classification inferred from diagnostic imaging evidence was the single nodular type in 16 cases, the multiple nodular type in 10 cases, and the massive type in 3 cases. The size of the single nodular tumor was 2 cm or less in 3 cases, 2–5 cm in 9 cases, and 5 cm or more in 4 cases. For the massive-type lesions, the maximal diameter was 7–12 cm.

The TNM classification [3] showed lesions of stage I in 3 patients, stage II in 14 patients, stage III in 6 patients, and stage IV in 6 patients. Stage II or less-severe lesions were found in 58.6% of the patients (Table 1). Lesions classified as Child A were clearly much more common, occurring in 23 patients, as compared with Child B disease in 5 patients and Child C disease in 1 patient.

The survival data were further analyzed in relation to the use of Lipiodol. Of the 228 patients who did not receive Lipiodol, only 6 survived for 5 years or more, whereas 23 (79.3% of all patients who survived for 5 years or more) of the 215 patients who also received Lipiodol survived for 5 years or more. As shown in Table 2, all patients with

stage III or IV disease also received Lipiodol, whereas all patients who survived for 5 years or more after TCE without Lipiodol had stage I or II disease.

Discussion

It used to be believed that the life expectancy of many patients with nonresectable HCC was only several months [2, 12]. However, with recent advances in diagnostic techniques and treatment, this notion has become outdated. One of the reasons for the increased life expectancy of patients with nonresectable HCC is no doubt the development of TCE therapy. The 5-year cumulative survival rate was 8% in our study, which had not been thought possible before the introduction of TCE. As had previously been reported [9], Lipiodol further increased the survival rate. This retrospective study, which analyzed data from many patients, made the benefits of Lipiodol even more obvious. With its use, the 5-year survival rate improved from 3.4% (without Lipiodol) to 12.9%.

Analysis of the demographic data on the patients who survived for 5 years or more showed that those in their 50s comprised the largest proportion (41%), followed by patients in their 70s (28%). In the macroscopic classification, single nodular lesions were predominant (55%), and 75% of these lesions measured 5 cm or less in diameter. It is obvious that the smaller the single nodular lesion, the better the prognosis. The prognosis is always good for lesions measuring 5 cm or less in diameter, whether surgery or embolization is used to treat them [11, 16].

Tsunoda et al. [16] reported that 13 of 16 patients who survived for 5 years or more following hepatectomy had had lesions measuring 5 cm or less in diameter. The noteworthy difference between surgery and TCE in the present study is that among 17 (58.6%) of the 29 patients who survived for 5 years or more, 4 had a single lesion measuring 5 cm or more in diameter, 10 had multiple lesions, and 3 had massive lesions with obvious portal invasion. That is, TCE was successful in these 17 patients whose prognosis would have been very poor if they had been treated by surgery.

Another important point, which cannot be expected from surgery, is that 6 patients each with TNM stage III and IV lesions, accounting for 41%, were included in the 5-year survivors, although stage II disease was common, and 59% of the patients had stage II or stage I lesions.

In three patients with stage III or IV (massive-type) disease who also had portal invasion, the blood flow was blocked in both the hepatic artery and the portal vein following TCE. Thus, the portal occlusive region, including noncancerous tissues, seemed to be exposed to the very potent cytotoxic effect of chemoembolization. The cytotoxic effect that was potentiated by enhanced exposure in the tumor tissue might have contributed to the long-term survival of these patients.

Child A lesions were very common (79%). The hepatic function level before TCE is one of the important prognostic factors.

In all, 23 of the patients (79%) who survived for 5 years or more also received Lipiodol. The survival curves indicate that Lipiodol contributed greatly to long-term survival following TCE (Fig. 2). The use of Lipiodol was further analyzed in relation to the TNM stage. All patients with stage III or IV disease received Lipiodol. Lipiodol is known to be effective in intrahepatic metastases and intraportal tumor thrombi, which are common in HCC. It has also been reported that the response to TCE without Lipiodol is not very good [6]. The present study supports the results of earlier investigations.

We speculate that the improved response obtained when Lipiodol is added to TCE may be related to the slow topical release of the anticancer drug given at a high concentration. Lipiodol and an anticancer drug are given in the form of a water-in-oil emulsion [9]. As they then stay in the tumor and surrounding tissues for a long time and partly flow into the portal vein [8], the anticancer drug is slowly released into the tumor tissue at a high concentration.

In conclusion, TCE helped to prolong the life of patients with HCC. It should be emphasized that TCE with Lipiodol contributed greatly to the improved cumulative 5-year survival rate obtained in these patients with advanced HCC.

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