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Historical changes of hospitalization in patients with hepatocellular carcinoma considering for clinical path preparation

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Abstract : We examined the hospitalization time in 346 patients with hepatocellular carcinoma who were treated between January 1991 and March 2002 (486 admissions). A newly introduced IVR CT system and an advanced catheter shortened the mean time from 65.0 (1991) to 35.6 (2001) days in patients who underwent transcatheter arterial embolization (TAE). For patients having TAE combined with percutaneous ethanol infusion (PEI), the mean time was shortened from 156.5 to 48.7 days. In those who underwent PEI, the values were 56.0 and 36.8 days, respectively. In those who underwent radio frequency ablation (RFA), the mean time in 2001 was 25.3 days. Overall, the mean time was shortened from 60.5 to 38.0 days. In particular, the mean time (41.0 days) after 1999, when the IVR CT system and RFA were introduced, was significantly shorter than that before their introduction (58.9 days). Advances in instruments and procedures for TAE have greatly shortened the hospitalization period. In patients who underwent PEI, the rate of decrease in the mean time was small and it is difficult decrease their length of hospital stay ; therefore, RFA may be frequently employed in the future. J. Med. Invest. 54 : 124-132, February, 2007

Keywords **:** *hepatocellular carcinoma, hospitalization period, crinical path, Interventional-radiology computed-tomography/angio system*

INTRODUCTION

Marked advances in the diagnosis and treatment of hepatocellular carcinoma (HCC) have prolonged survival. However, recurrent HCC and the exacerbation of liver cirrhosis, an underlying disease, require frequent admissions, leading to prolonged admission for many patients (1, 2). In HCC treatment, if the hospitalization period could be shortened, a significant improvement might result in patient quality of life.

In 2003, Diagnosis Procedure Combination (DPC) was introduced for specific hospitals, and will be applied throughout Japan. Shortening of the hospitalization period is emphasized as an important issue for hospital management. Clinical path procedures have been introduced in an increasing number of hospitals to reduce the hospitalization period.

In the field of HCC treatment, clinical paths for transcatheter arterial embolization (TAE), radio frequency ablation (RFA), and resection have been introduced in an increasing number of hospitals. However, in many patients with HCC, treatment is not selected on admission ; in most hospitals, therapeutics strategies are determined after hematology and imaging procedures such as abdominal angiography

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and computed tomography (CT) under angiography are performed after admission. This allows for the detailed examination of the HCC status and background hepatic reserve. As well, treatments for HCC vary : transarterial procedures such as TAE, percutaneous procedures such as percutaneous ethanol infusion (PEI), resection, and liver transplantation. In some patients, treatment is not completed by a single therapy. There appears to be no consensus regarding treatment selection. The recent development of new equipment such as the Interventional-Radiology computed-tomography/angio system (IVR-CT system) (3), which facilitates the simultaneous accomplishment of CT and serial angiography, and procedures including RFA, is changing diagnostic and treatment procedures.

Several studies have reported hospitalization times for a single therapy such as RFA and TAE, but no study has investigated it for HCC treatment as a whole. Here, we examine changes in the time from admission until discharge in HCC patients, the reasons for changes in time, tumor state/treatment-related differences and hepatic reserve. We also investigate whether the new diagnostic IVR-CT system and a new treatment procedure, RFA, shortens the hospitalization period. As well, we reviewed whether the future introduction of clinical path procedures would further shorten the interval.

PATIENTS AND METHODS

The subjects were 346 patients with HCC who underwent internal medicine treatment because of difficulties or refusal related to surgical treatment between January 1991 and March 2002 (total : 486 admissions). Patients were divided into 2 groups (early and late phase groups) by the time of treatment, before and after September 1999, when the IVR-CT system and RFA were introduced. With respect to treatment, they were divided into 4 groups : a TAE group in which transarterial procedures such as selective transcatheter arterial embolization (s-TAE) were performed ; a PEI group in which PEI was performed ; a TAE+PEI group in which PEI was additionally performed due to the less marked local curative effects of a transarterial approach, or PEI was additionally performed to treat HCC in another site following a transarterial approach ; and a RFA group in which RFA was performed. We also investigated the hospitalization period with respect to hepatic reserve (Child-Pugh classification), tumor factors including the number of tumors and maximum tumor diameter. In patients with advanced HCC (stage Ⅳ-A), which requires long-term admission, we investigated the hospitalization period with respect to treatment procedures and hepatic reserve. For tumor staging we used the general rules for the clinical and pathological study of primary liver cancer (4).

In patients in whom varix treatment was concurrently performed, we reviewed the period during which they were admitted to treat HCC. We excluded patients with extrahepatic metastasis, as systemic chemotherapy and radiotherapy targeted another lesion other than HCC.

In selecting treatment, CT under portography and CT under hepatic arteriography (CTHA) were performed (5, 6). When the entire tumor was stained on CTHA, a transarterial treatment such as s-TAE was selected. About 2 weeks after treatment, we evaluated the treatment response. When there were less marked local curative effects, PEI or transarterial treatment was additionally performed. Treatment was continued in accordance with the hepatic reserve until complete necrosis was achieved. We also selected PEI or RFA for patients in whom tumors were not stained on CTHA, and those in whom marked flexion and narrowing of the hepatic artery made it difficult to selectively insert a catheter into the segmental/subsegmental vessels. PEI was performed twice a week if possible. The choice of treatment for patients with advanced HCC (stage Ⅳ-A) was determined by a similar procedure.

For treatment, tumor factors including the number of tumors and tumor diameter were not limited. However, treatment was discontinued in patients in whom improvement in the prognosis was considered difficult. In patients with a poor hepatic reserve, adjuvant therapy was performed prior to treatment to improve their hepatic conditions.

In this study, all patients who underwent transarterial procedures such as conventional TAE via the hepatic artery, s-TAE, and chemolipiodolization were assigned to the TAE group. In this group, patients who underwent s-TAE accounted for approximately 70%, followed by chemolipiodolization, and conventional TAE. In the TAE+PEI group, PEI was additionally performed in 66 patients, as complete necrosis was not achieved despite transarterial treatment for large tumors. In the other 40 patients, PEI was performed to treat another lesion.

The hospitalization period was expressed as the mean±standard deviation. Significance was tested between 2 groups using Mann-Whitney's U-test. Val-

ues were compared among several groups using the Kruskal-Wallis test. When there was a significant difference, Bonferroni's test was employed. A p value was less than 0.05 ($p<0.05$) was regarded as significant. These tests were conducted using Stat View 4.5 software (SAS Institute Inc., U.S.A.).

RESULTS

The early phase group consisted of 205 patients. The total frequency of admission was 283 times (initial treatment : 157 patients, relapse treatment : 126). The late phase group consisted of 141 patients. The total frequency of admission was 203 times (initial treatment : 98 patients, relapse treatment : 105). Patient background, tumor type, treatment procedures, and treatment responses are summarized in Table 1. In our patients with HCC who were treated during the study period (10 years), the 1-year, 5-year, and 10-year survival rates were 85.6%, 31.2%, and 11.9%, respectively. As shown in Fig. 1, the early phase group was compared with the late phase one. The mean hospitalization period in HCC late phase patients (41.0 days) was significantly shorter than that in early phase ones (58.9 days). In the PEI group, the mean times were 45.9 and 41.4 days in the early and late phases, respectively. In the TAE group, the mean times were 61.8 and 36.7 days in the early and late phases, respectively. In the TAE +PEI group, the mean times were 81.0 and 53.5 days in the early and late phases, respectively. In the TAE group and TAE+PEI group, the mean time was significantly shorter in the late phase than in the early.

The hospitalization period in each treatment group with respect to maximum tumor diameter is shown in Table 2. In the PEI group, the mean times in the early and late phases in patients with tumors measuring 3 cm or less were 46.3 and 39.3 days, respectively. In those with tumors measuring 3 to 5 cm, there were no changes. In those with tumors measuring 5 cm or more, the mean interval was prolonged from 49.0 to 78.3 days. In the TAE group, the mean hospitalization period was shortened regardless of the tumor diameter. There was a significant difference between the early phase and late phase groups in patients with tumors measuring 3 to 5 cm. In the RFA group, the mean times were 25.2 and 20.9 days in patients with tumors measuring 3 cm or less and

Table 1. Patient background

		Early phase group	Late phase group	
Number of patients		205	141	
Frequency of admission		283	203	
Age (mean age)		43～87(65.1)	49～83(68.3)	$p<0.001$
Gender	Male	188	135	ns
	Female	95	68	
Hepatic reserve	A	49	78	$p<0.001$
Child-Pugh classification	B	146	84	
	C	88	41	
Number of tumors	1	151	108	ns
	2	60	38	
	3	23	22	
	Many	49	35	
Maximum tumor diameter (cm)	3 or less	200	140	ns
	3 to 5	48	43	
	5 or more	35	20	
Tumor Stage	Ⅰ	75	54	ns
	Ⅱ	67	62	
	Ⅲ	45	27	
	Ⅳ-A	96	60	
Treatment	PEI	125	76	$p<0.0001$
	TAE	97	63	
	TAE+PEI	61	45	
	RFA	0	19	
Treatment response	Complete necrosis	196	154	ns
	Incomplete necrosis	87	49	

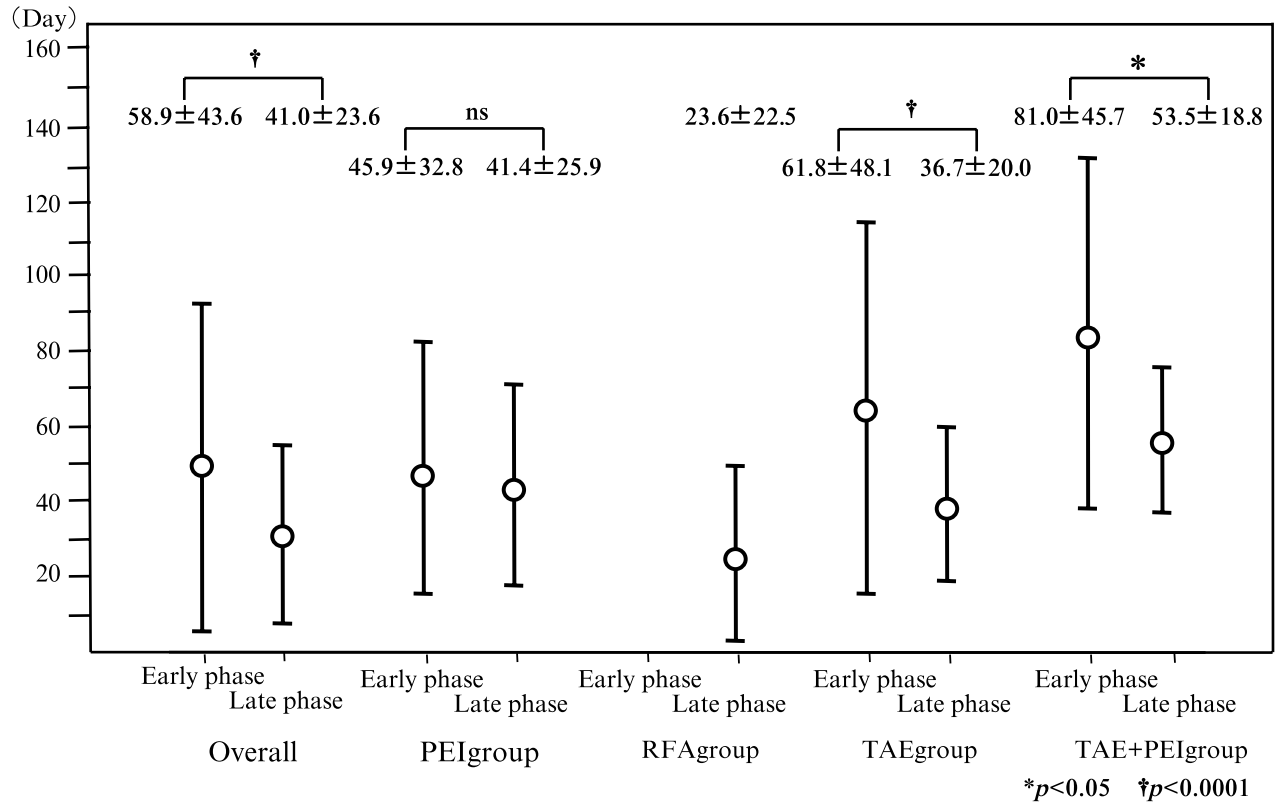

Fig. 1 Hospitalization period in the early and late phase groups
The hospitalization period was expressed as the mean±standard deviation. In the PEI group, the mean time were 45.9 and 41.4 days in the early and late phases, respectively, with no significant difference. In the TAE group and the TAE+PEI group, the mean time in the late phase was significantly shorter than that in the early phase.

Table 2. Hospitalization period in each treatment group with respect to maximum tumor diameter

		~3		3~5		5~		(cm)
PEI	Early phase	46.3±34.1(111)	ns	42.0±19.8(12)	ns	49.0±26.9(2)	ns	
group	Late phase	39.3±24.7(63)		43.7±18.5(10)		78.3±48.4(3)		
TAE	Early phase	59.8±54.0(59)	*	60.0±40.4(20)	ns	70.3±34.7(18)	*	
group	Late phase	33.6±17.3(41)		42.6±24.6(14)		42.8±19.5(8)		
RFA	Early phase	–		–		–		
group	Late phase	25.2±28.0(12)		20.9±8.6(7)		–		
TAE+PEI	Early phase	76.6±50.2(30)	ns	85.6±53.0(16)	ns	89.5±29.7(15)	*	
group	Late phase	53.5±20.7(24)		54.2±17.0(12)		52.7±17.9(9)		

*$p<0.05$

The hospitalization period was expressed as the mean±standard deviation.
A number in a parenthesis shows the number of patients.

those with tumors measuring 3 to 5 cm, respectively. In the TAE+PEI group, the mean hospitalization period was shortened for all tumor diameters. This tendency was more marked in patients with larger tumors. There were significant differences between the early and late phase groups in those patients with tumors measuring 5 cm or more.

The hospitalization period in each treatment group with respect to number of tumors is shown in Table 3. In the PEI group, the mean interval was shortened in patients with 2 tumors or with 4 or more tumors. However, there was no shortening in those with 1 or 3 tumors. In the TAE group, the mean hospitalization period was shortened regardless of the tumor number. There was a significant difference between the early phase and late phase groups in patients with 3 tumors. In the RFA group, the mean times were 20.9 and 38.0 days in patients with a single lesion and those with 2 lesions, respectively. In the TAE+PEI group, the mean time was shortened in most groups. However, it was prolonged in those patients with 3 lesions.

Concerning the hepatic reserve, the times were 42.3±27.8 days in Child-Pugh A patients, 53.8±41.0

days in Child-Pugh B patients, and 56.3±38.0 days in Child-Pugh C patients ; the mean time was shorter in patients with a better hepatic reserve, and there was a significant difference between Child-Pugh A and B groups, and between Child-Pugh A and C groups. Among Child-Pugh A patients, the mean times were 43.6±36.9 and 37.8±19.5 days in the early and late phase groups, respectively. Among Child-Pugh B patients, the values were 60.6±46.1 and 41.8±26.4 days, respectively. Among Child-Pugh C patients, the values were 61.5±42.1 and 45.2±24.3 days, respectively. In all patients in late phase groups the mean interval was shortened. In Child-Pugh B patients, there was a significant difference between the early phase and late phase groups.

In the early phase, 64 patients with stage Ⅳ-A HCC were treated, with a total frequency of admission of 96. In the late phase, 39 stage Ⅳ-A patients were treated, with a total frequency of admission of 60. The incidence of solitary lesions was higher in the early phase group, possibly because many patients showed portal invasion (Table 4). In stage Ⅳ-A patients, the early and late phase groups, the mean times were 67.1 and 50.0 days, respectively, showing a significant difference. For treatment procedures, mean times were shortened in all groups. However, in the PEI group, there was no significant difference between the early and late phase groups (Fig. 2). In respect to hepatic reserve, the times were 47.0±26.2 days in Child-Pugh A patients, 61.0

Table 3. Hospitalization period in each treatment group with respect to number of tumors

		1		2		3		Many	
PEI	Early phase	41.7±31.0(89)	ns	48.7±24.1(21)	ns	67.6±52.6(7)	ns	66.3±42.4(8)	ns
group	Late phase	39.1±26.6(48)		32.9±11.8(15)		65.9±24.7(10)		37.7±10.8(3)	
TAE	Early phase	59.2±56.3(46)	*	58.4±37.3(17)	*	74.8±45.4(6)	ns	65.4±40.7(28)	*
group	Late phase	33.1±19.3(29)		31.4±18.8(8)		56.6±24.7(5)		39.0±18.8(21)	
RFA	Early phase	—		—		—		—	
group	Late phase	20.9±21.4(16)		38.0±27.5(3)		—		—	
TAE+PEI	Early phase	83.2±41.2(16)	*	87.2±50.0(22)	ns	54.6±26.6(10)	ns	88.3±51.8(13)	ns
group	Late phase	46.5±16.3(15)		55.7±22.6(12)		60.4±19.9(7)		56.2±16.3(11)	

*$p<0.05$

The hospitalization period was expressed as the mean±standard deviation.
A number in a parenthesis shows the number of patients.

Table 4. Background factors of stage Ⅳ-A patients

		Early phase group	Late phase group	
Number of patients		64	39	
Frequency of admission		96	60	
Age (mean age)		43～83(64.8)	49～82(68.9)	$p<0.001$
Gender	Male	62	38	ns
	Female	34	22	
Hepatic reserve	A	11	20	$p=0.14$
Child-Pugh classification	B	51	25	
	C	34	15	
Number of tumors	1	11	2	ns
	2	27	17	
	3	17	13	
	Many	41	28	
Maximum tumor diameter (cm)	3 or less	53	33	ns
	3 to 5	22	14	
	5 or more	21	13	
Treatment	PEI	24	14	ns
	TAE	40	25	
	TAE+PEI	32	20	
	RFA	0	1	
Treatment response	Complete necrosis	35	28	ns
	Incomplete necrosis	61	32	

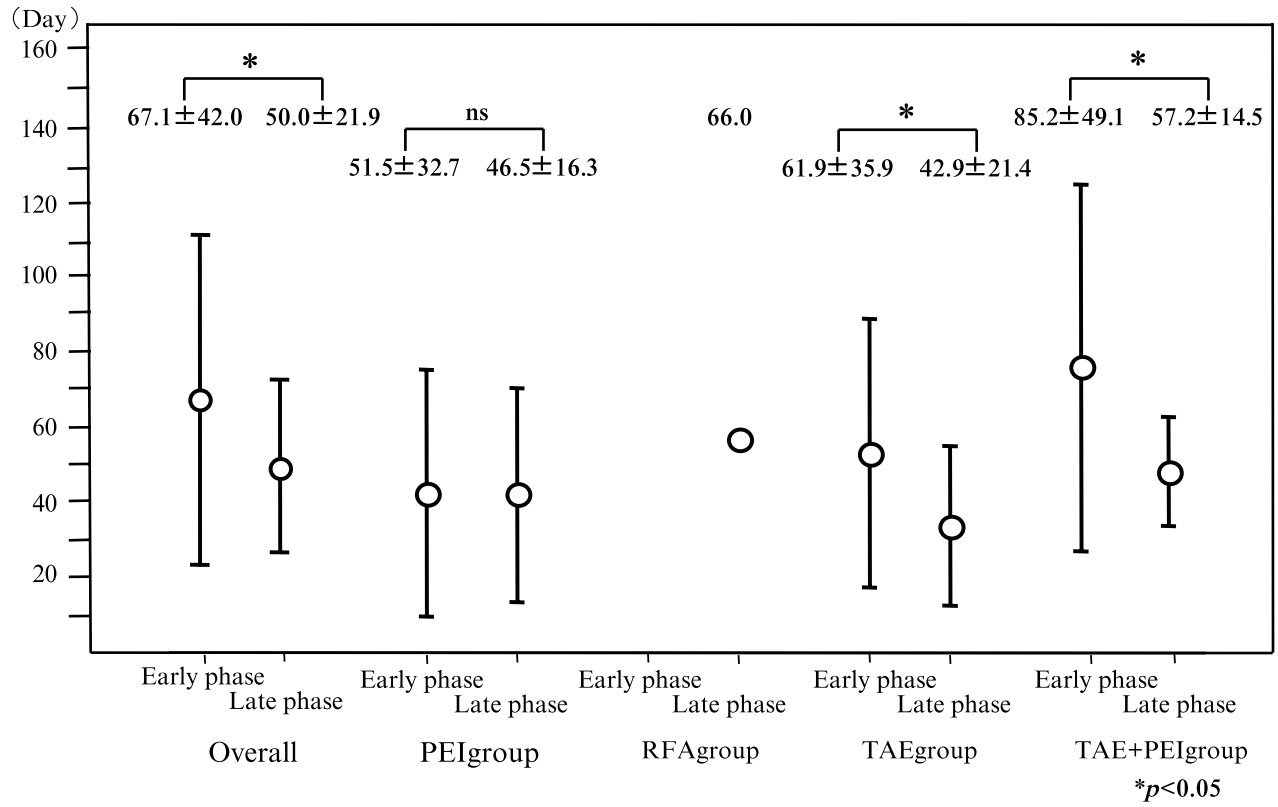

Fig. 2 Stage Ⅳ-A patients : Hospitalization period in the early and late phase groups
The hospitalization period was expressed as the mean±standard deviation. For treatment procedures, mean times were shortened in all groups. However, in the PEI group, there was no significant difference between the early and late phase groups

±39.4 in Child-Pugh B patients, and 68.4±35.5 in Child-Pugh C patients ; the mean time was shorter in patients with a better hepatic reserve, and there was a significant difference between the Child-Pugh A and C groups. Among Child-Pugh A patients, the times were 53.6±36.9 and 43.6±18.1 days in the early and late phase groups, respectively. Among Child-Pugh B patients, the values were 67.2±45.0 and 48.3±19.2 days, respectively. Among Child-Pugh C patients, the values were 71.3±38.7 and 61.8±26.9 days, respectively. In all late phase groups, the mean time was significantly shortened.

DISCUSSION

Sackett, *et al.* reported that it was important to follow 5 steps of problem extraction, information investigation, critical review, performance, and evaluation, for preparing a clinical path based on the EBM (7). This study corresponds to the first step (problem extraction), and we investigated the hospitalization times required for HCC treatment and its limitations.

In our PEI group, the hospitalization period saw no further reduction after 1997. With respect to tumor diameter, the interval was prolonged in patients with tumors measuring 3 cm or more. From this examination, PEI may not be a preferred method for treating large tumors. The infusion dose per shot was increased, and several punctures per session were performed. However, these strategies did not markedly contribute to any shortening of the hospitalization period. PEI was developed by Sugiura, *et al.* in 1983(8). Since then, a multiple-needle insertion technique (9) and a CT-assistance method have been reported. However, basically, neither instruments nor procedures have improved since ; thus there was no marked decrease in the hospitalization period. In essence, PEI may have been developed as a complete procedure that can not be further improved and so it is unlikely that any marked shortening of the hospitalization period will be seen in the future. Indeed, RFA may be the method mainly employed for percutaneous treatment. However, PEI may still be applicable for treating small tumors and those adjacent to other organs, the bile duct, and blood vessels. Strategies for shortening the hospitalization period must be established.

TAE was initially reported by Yamada, *et al.* in 1983(10). Since then, Segmental Lipiodol-TAE has been developed (11). The interval was markedly

shortened after 1998, that is, before the IVR-CT system was introduced. This was possibly because new devices such as a selective guide-wire and flexible catheter were developed in 1998 (12), and introduced in our department. The IVR-CT system may have contributed to a decrease in the hospitalization period between 1998 and 1999. The appearance of these new devices including the IVR-CT system has facilitated TAE via the cancer-bearing artery and multi-segmental TAE in which TAE is simultaneously performed via several responsible blood vessels (13, 14). Complete necrosis of the lesion has increasingly been achieved by a single course of TAE even in patients with large HCC lesions, and those with multiple lesions.

RFA facilitates more extensive ablation per course compared to microwave ablation therapy. It more accurately achieves tumor necrosis compared to PEI (15), and is now being introduced in many hospitals. In some hospitals, a clinical path has been established, and the hospitalization period shortened to 1 week or less. Recently, some studies have reported that RFA prolongs survival in comparison with PEI (16, 17). In an increasing number of hospitals, RFA has been selected as a first-choice percutaneous treatment. As well, several studies have established an extensive area of ablation for large HCC lesions to enable ablation to be completed by a single course of RFA (18, 19). RFA will be mainly employed as the percutaneous treatment in the future.

In TAE+PEI therapy, the addition of PEI is performed to treat intra-capsular/extra-capsular infiltration and that immediately below the capsule or around the septum, for which TAE alone is less effective (20-22). In this group, the proportion of patients with advanced tumors in whom it was difficult to continue treatment until complete necrosis was achieved was higher than those in the other groups. We treated only HCC lesions that might rupture, and the minimum treatment for improving the prognosis was initially planned for early discharge, which may have contributed to a marked decrease. With respect to tumor factors, the interval was prolonged in patients with 3 tumors. This patient group showed the highest tumor count among those for which complete necrosis can be targeted, 1 to 3, and so treatment targeting complete necrosis may have prolonged the time.

TAE and TAE+PEI were performed in 45% and 32%, respectively, of Stage Ⅳ-A patients ; many were treated by transarterial procedures. Complete necrosis was achieved in 71% of HCC patients ; however, it was achieved in only 38% of Stage Ⅳ-A patients. In Stage Ⅳ-A patients, the length of hospitalization was about 20% longer than that in the HCC patients. However, over the past 10 years it has been shortened to approximately 60%.

The hospitalization period was shorter in patients with a better hepatic reserve. This was because treatment per course was limited in those with a poor hepatic reserve, increasing the frequency of treatment and prolonging the treatment interval. Even in patients with a poor hepatic reserve, the accurate treatment-related reduction of the grade of disorders of the normal liver tissue shortened the hospitalization period.

Issues that are not directly related to medical practice may also influence the hospitalization period : the bed-waiting interval until examination is not constant ; and the intervals between examination and treatment, between treatment and response evaluation, and between response evaluation and discharge are not efficiently established. To overcome such limitations, a system to establish clinical paths needs to be established. For TAE, patients are admitted the day before angiography, and the lesion site is photographed using the IVR-CT system after the end of treatment. When sufficient treatment has been accomplished, patients are discharged 7 to 10 days after treatment. Treatment response is evaluated at the outpatient clinic. For PEI, patients are admitted the day before angiography, and percutaneous treatment is performed the day after angiography. On Days 3, 7, and 11, treatment is performed. On Days 10, 14, and 18, the treatment response is evaluated. Even when 3 courses of treatment are performed, patients may be discharged approximately 20 days after admission. For RFA, treatment is performed on Day 3, and the treatment response is evaluated on Day 6, as described for PEI. Treatment for TAE+PEI, is similarly performed. However, the interval between TAE and the initial course of PEI is established as 2 weeks, and PEI is performed on Days 16, 20, and 24. The treatment response is evaluated on Days 23, 27, and 31. Even when PEI is added 3 times, treatment is completed within 1 month of admission. If possible, RFA should be selected as an additional therapy.

When a clinical path is prepared as described above, the hospitalization period is 10 to 20 days for PEI, about 1 week for TAE and RFA, and 3 to 4 weeks for TAE+PEI. However, in our study, the intervals were 41.4, 36.7, 23.6, and 53.5 days, respectively, in the late phase group. This was because our

series included many patients requiring additional treatments, those with severe hepatopathy after treatment, and those with complications (23-25). When establishing a clinical path, these patients may be dropped as variances. Standard deviations were 17.6, 20.6, 16.3, and 26.6 days in the TAE, PEI, TAE+PEI and RFA groups, respectively. They clearly decreased year by year. However, there were still marked differences. Thirty-eight episodes in the early and 5 episodes in late phase groups required more than a 100-day period for admission. Seventeen episodes were for patients with TAE+PEI and 15 episodes were patients with TAE in the early phase group, and one was a patient with TAE+PEI in the late phase group. The situation where hepatic failure appeared after treatment, and where hospitalization continued to next treatment was the majority one. It may be realistic to undertake examination and treatment in another hospitalization, and for patients in TAE+PEI group to be discharge in the interim between TAE and PEI. In preparing a clinical path, the above issues need to be considered. For a hospitalization practice for HCC, strategies must be established to shorten the length of the hospitalization. As well, issues should be reviewed at the next step by introducing a clinical path. If a standard clinical path is finally prepared, it would have benefits for HCC patients and for the medical professionals charged with hospital management.

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