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Validating a Markov Model of Treatment for Hepatitis C Virus-related Hepatocellular Carcinoma

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Summary

Objective: We created and validated a Markov model to simulate the prognosis with treatment for HCV-related hepatocellular carcinoma (HCC) for assessment of cost-effectiveness for alternative treatments of HCC.

Method: Markov state incorporated into the model consisted of the treatment as a surrogate for HCC stage and underlying liver function. Retrospective data of 793 patients from three university hospitals were used to determine Kaplan-Meier survival curves for each treatment and transition probabilities were derived from them.

Results: There was substantial overlap in the 95% CIs of the Markov model predicted and the Kaplan-Meier survival curves for each therapy. The predicted survival curves were also similar with those from the nationwide survey data supporting the external validity of our model.

Conclusions: Our Markov model estimates for prognosis with HCC have both internal and external validity and should be considered applicable for estimating cost-effectiveness related to HCC.

Keywords

Hepatocellular carcinoma, prognosis, survival rate, Markov model, validation

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1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common forms of carcinoma and the incidence is increasing in Japan and other countries [1, 2]. Accordingly, the burden of HCC on health resources has risen considerably and the differences in the effect and cost of the specific treatments or periodic surveillance program for HCC has been given increasing attention.

HCCs in most cases originate from a fibrotic lesion in the liver and more than 70% of them are caused by hepatitis C virus (HCV), with some caused by hepatitis B virus (HBV) or other conditions, such as alcoholic liver injuries, in Japan [1]. Although several treatment standards for HCC have been proposed [2, 3], due to the absence of large randomized trials, the current treatment strategy for HCC remains a matter of choice, depending mostly on retrospective studies [4]. Treatments for HCC have been progressing using current technology, such as echo-guided needle insertion and catheterization into the hepatic artery. Thus, we need to establish a method to evaluate the survival benefit of each treatment. Moreover, another characteristic feature of HCC is its frequent recurrence, even after successful treatment, and the duration between a recurrence and subsequent recurrence tends to be short in the progression. These natures make it difficult to evaluate the superiority among treatments or appropriate one according to the conditions of HCC. To compensate for the lack of apparent evidence related to the treatment, a predicting prognostic computer simulation model could be a solution, but few such models for HCC that deal with the frequent recurrences and have been appropriately validated have been reported to date.

The aim of this study was to develop and validate a simulation model to predict the prognosis after initial treatments for HCV-related HCC using clinical data.

2. Method

2.1 Patients

We retrospectively studied the medical records of the patients admitted for the initial treatment of HCC between January 1994

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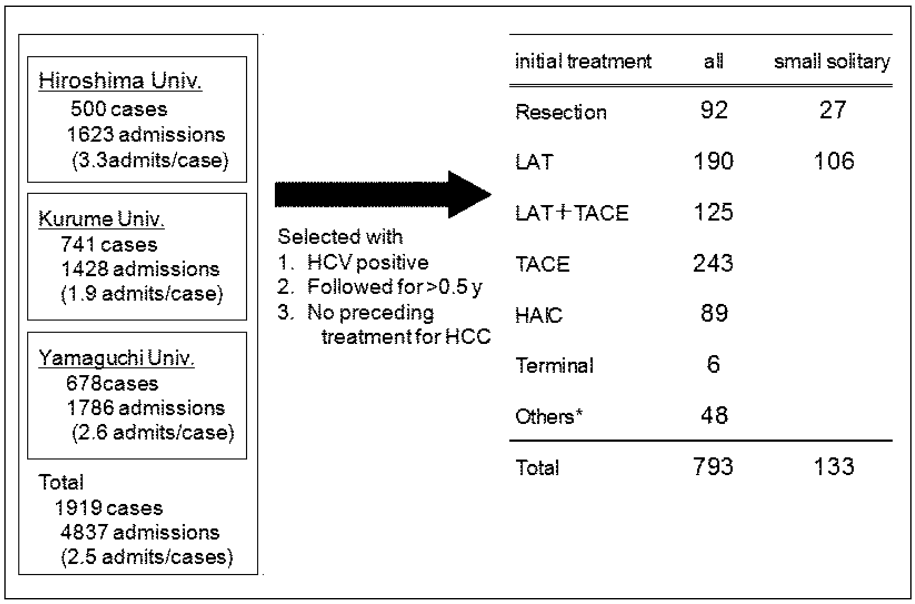

Fig. 1 Retrospective survey of HCC cases among three universities. * Others included combination of three treatment, combination of resection and LAT, and combination of resection and TACE.

and December 2003 at the three university hospitals; Yamaguchi, Hiroshima and Kurume. Total subjects were 1913 cases with 4837 admissions (Fig. 1).

The inclusion criteria were naïve HCV-related HCC cases with a follow-up period of more than half a year after the first admission. Total of 793 patients were eligible. They had an average 3.1 admissions (range: 1-17) and were followed for an average of 37 months (range: 181-3920 days). Among these patients, initial treatment by hepatic resection (HR), local ablation therapy (LAT), combination therapy of LAT and transcatheter arterial chemoembolization (TACE), TACE monotherapy, hepatic artery infusional chemotherapy (HAIC) or systemic chemotherapy and supportive treatment for terminal state were indicated for 92, 190, 125, 243, 89 and 6 patients respectively.

The average age of the patients was 64.7 years old (range: 40-83), male ratio was 0.62 and the proportion of liver cirrhosis was 0.89. The other characteristics were presented in Table 1. They were maximal size and number of tumors, the proportion of cases with previous history of interferon therapy, ratio of involvement with portal vein, hepatic artery or vein, or biliary duct, vascularity of tumor, total follow-up period, average number of admission and number of attained complete remission state and duration of it. Limiting the population to solitary and small tumors (less than 3cm in maximum diameter) as an early HCC state,

Table 1 Baseline characteristics of the cases

Initial treatment		HR (N = 92)		LAT (N = 190)		LAT + TACE (N = 125)		TACE (N = 243)		HAIC (N = 89)		Terminal (N = 6)		Others* (N = 48)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age		63.4	8.3	66.2	8.3	66.5	7.7	65.8	7.4	65.6	6.3	62.7	11.9	66.4	8.0
Male ratio		0.83		0.64		0.67		0.70		0.81		0.67		0.75	
Tumor	Max. size	3.99	2.79	2.18	2.69	2.36	1.03	3.88	2.72	5.10	3.53	4.05	2.32	3.08	2.36
	Number**	1.71	1.35	1.52	0.89	2.31	1.91	3.04	2.91	6.16	6.08	2.83	1.60	2.83	2.21
IFN treatment before admission (rate)		0.23		0.14		0.11		0.06		0.05		0.00		0.16	
Involvement of vessels (rate)		0.23		0.05		0.02		0.14		0.27		0.33		0.19	
High vascularity of tumor (rate)		0.92		0.72		0.89		0.97		0.99		0.83		0.93	
Total FU*** (day)		1339	862	1255	866	1309	815	1026	770	682	529	404	295	1243	891
No. of admission		2.28	1.95	2.87	2.08	3.85	2.28	3.41	2.03	2.13	1.44	1.67	0.52	3.46	2.74
No. of CR#		1.27	0.76	1.29	0.98	1.08	1.14	0.67	0.94	0.37	0.77	0.00	0.00	0.58	0.85
CR duration (day)		922	836	709	691	501	598	359	626	142	351	0	0	287	488
CR	Rate/admission	0.71	0.36	0.56	0.38	0.32	0.33	0.22	0.31	0.16	0.31	0.00	0.00	0.20	0.31
	Duration/total FU	0.68	0.34	0.55	0.36	0.33	0.33	0.25	0.35	0.13	0.28	0.00	0.00	0.22	0.33

* include combination of three treatments, combination of resection and LAT, and combination of resection and TACE
** In case that more than ten nodules were seen, its number of tumors was treated as 11 nodules.
*** follow-up periods
# complete remission after treatment

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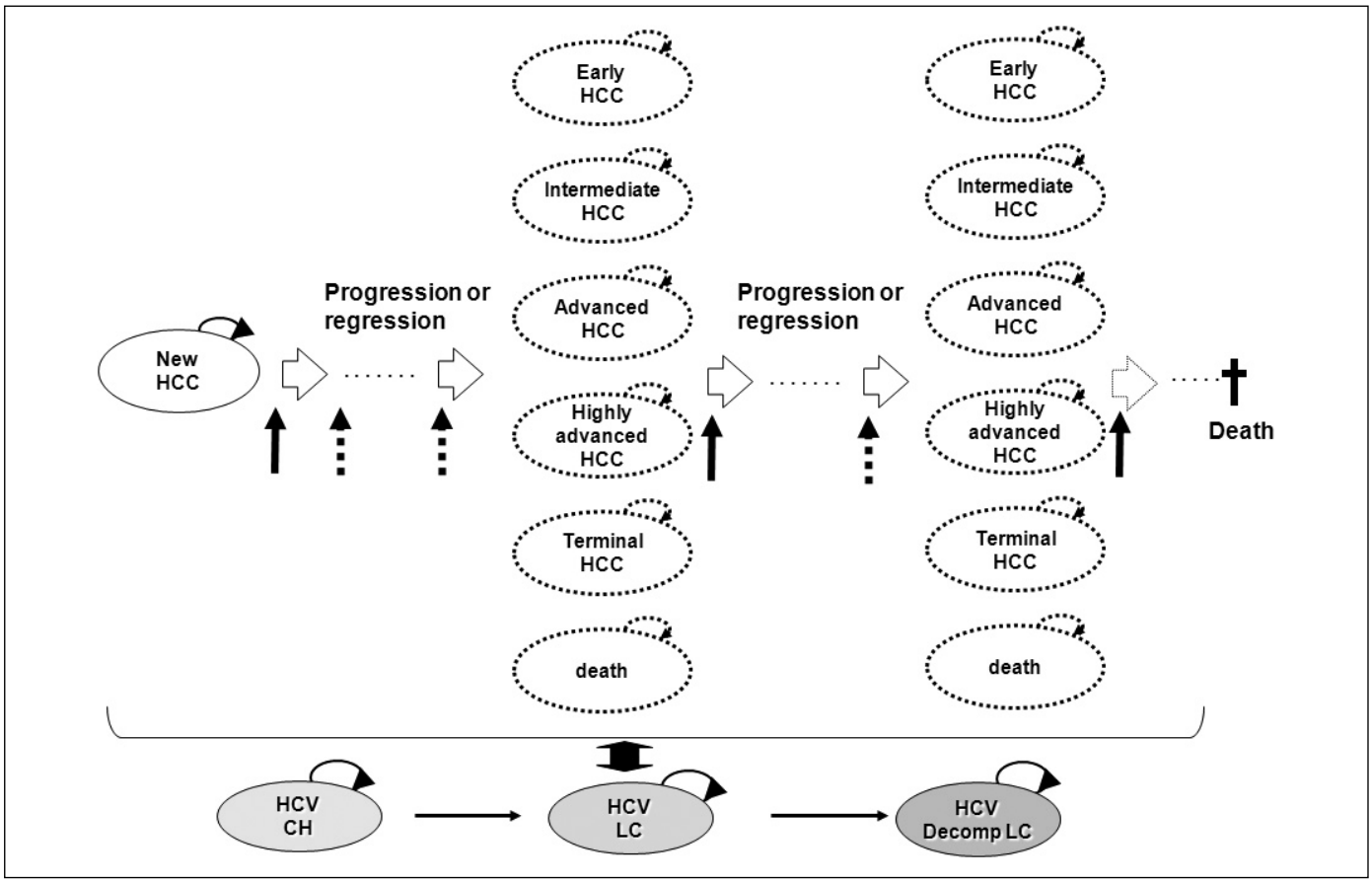

Fig. 2 Schema of the Markov model of treatment for HCC. Solid vertical arrows indicate optimal treatments according to HCC characteristics and preserved liver function, and dashed vertical arrows indicate the same treatments undertaken optionally for the same state of HCC. Outlined horizontal arrow indicates a Markov cycle representing progression or regression from one state to another at a constant transition probability in each cycle. Along with the transition of HCC state, underlying chronic hepatitis caused by HCV may also progress to a more advanced cirrhotic state.

we evaluated 27 of HR and 106 of LAT cases.

2.2 Development of a Markov Model According to Treatment Strategy

We developed a Markov model to predict prognosis of HCC patients to whom the different initial treatment options were indicated according to the tumor characteristics and preserved liver function. The Markov model is a multistate transition model that allows patients in a hypothetical cohort to make transitions among various health states, at different rates, over extended periods. In our model, the health states of treatment were represented as states of the Markov process. The schema of the Markov model (Fig. 2) represented possible transitions after initial treatment of HCC, and duration of each cycle was one-month. Figure 3 showed the model as a decision tree in which treatment arms were listed at the decision node and health states emanated from the Markov node. Once a patient entered the models the state of HCC might progress to a more advanced one by aggravation of HCC or regress to an improved one by efficient treatment, and also, underlying chronic hepatitis (CH), compensated liver cirrhosis (LC) or decompensated LC (decLC) might develop more advanced liver disease.

All Markov states led to the Markov subtree in a Markov cycle of one month (Fig. 4). The model consisted of two parts; one part was the initial HCC state that indicated the optimal treatment, and the other was the subsequent recurrence states. We defined the same HCC state that remained in the same condition or the status of complete remission, and the different HCC state that changed to another state due to recurrence or death from liver disease. We did not consider a direct treatment effect that is clinical judgment whether or not tumors were totally removed (complete remission). The reason is that it is not always possible to determine complete remission accurately.

2.3 Model Assumptions

Our model assumed that each optimal treatment was selected according to the tumor characteristics, such as size, number and existence of invasion to the portal vein,

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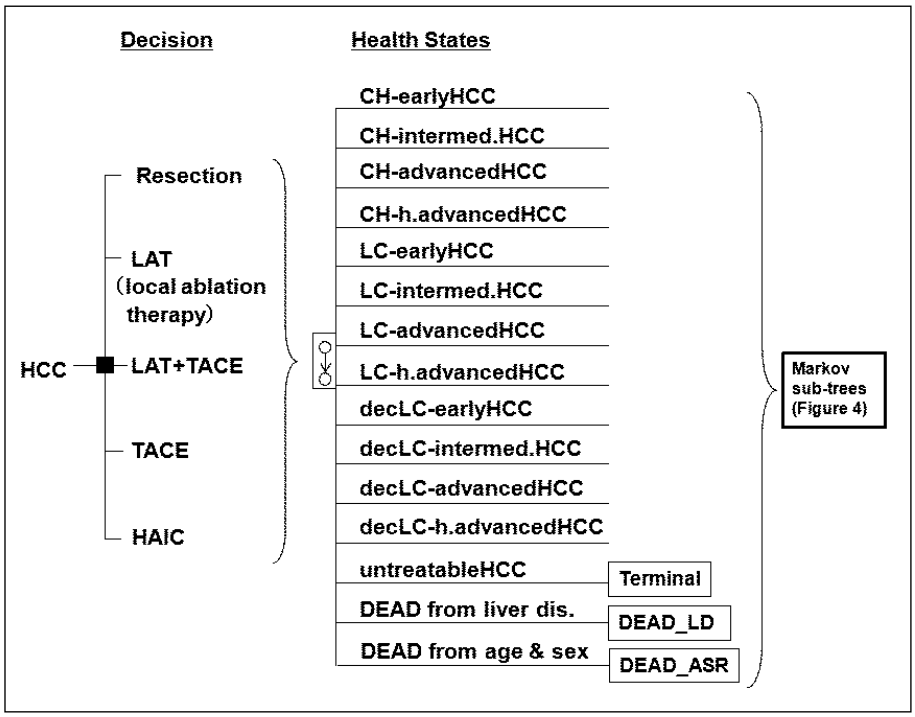

Fig. 3 Structure of decision tree with Markov process. Solid square indicates decision node of therapeutic procedures followed by Markov node (a rectangle with circles connected by an arrow) including 15 HCC (health) states. intermed.: intermediate, h.advanced: highly advanced

hepatic vein or biliary duct, and underlying liver state. In our treatment strategy, hepatic resection or LAT would be selected for the early HCC state (in general, small and solitary or oligo-nodules), combined therapy with LAT and TACE for the intermediate HCC state, TACE monotherapy for advanced HCC state, HAIC or systemic chemotherapy for highly advanced HCC state and supportive therapy for a terminal HCC state, respectively. In addition, the following assumptions were incorporated into the model.

1) The progression of underlying liver disease, such as CH to LC, LC to decLC, decLC to death occurs unrelated to the HCC state and the effect of treatment for HCC.
2) Patients in the HR groups undergo HR up to two times and they are subsequently eligible for LAT in case of early HCC.
3) In the case with decompensated liver cirrhosis, hepatic resection should not be selected, even for small solitary HCC, but LAT might be selected if preserved liver function would be tolerable.
4) Liver transplantation for HCC or decompensated liver cirrhosis was not incorporated into the model because such cases were so few in our data
5) We did not consider death caused by CH or compensated LC, except for the mortality rate for the general population by age and sex.

2.4 Estimation of Transition Probabilities and Rates of Next States

The length of transition of any HCC state was defined as the period from the date of admission for the treatment of some HCC state to the date of next admission for the different HCC state or to the date of death (Fig. 5).

The monthly transition probabilities were estimated separately by the cases from the group of initial treatment, and those from the group of recurrences. We obtained the median transition periods by nonparametric Kaplan-Meier (KM) method by treating transitions to different states including death related to liver disease as events data, and death unrelated to liver disease or withdrawal from follow-up as censored data. The median transition period was then converted into a monthly transition probability using the DEAL method [5, 6].

The rate of the next health state was calculated by the number of the state divided by the total number of the subsequent different states.

The transition probability of the terminal state to death was assigned equally, unrelated to underlying liver disease or HCC state, in which it was not possible to undergo any treatment for HCC, but only supportive therapy.

2.5 Progression of Underlying Liver Disease and Treatment-related Mortality

The annual progression rates from CH to compensated LC and compensated LC to decompensated LC were assigned values of 0.073 and 0.06, respectively, based upon previous studies [7].

Though we identified no case died within one month after any therapeutic procedure, we assigned the direct mortality rates caused by treatment procedure to be 0.008 for HR from the report of nationwide follow-up survey of primary liver cancer in Japan [8] and 0.001 for other treatments by experts' opinion.

2.6 Cohort Simulation

We analyzed the prognosis after initial therapy for the two categories of HCC cases as follows.

1) Early HCC cases (solitary and small tumor) that underwent hepatic resection or LAT.
2) Non-early cases that selected the combination therapy of LAT and TACE (LAT+TACE), TACE monotherapy or HAIC as the optimal initial treatment.

The simulation cohort had the same characteristics as the actual cases. The start age of the simulation was 65 years old, male ratio was 0.62 and the LC ratio was 0.89.

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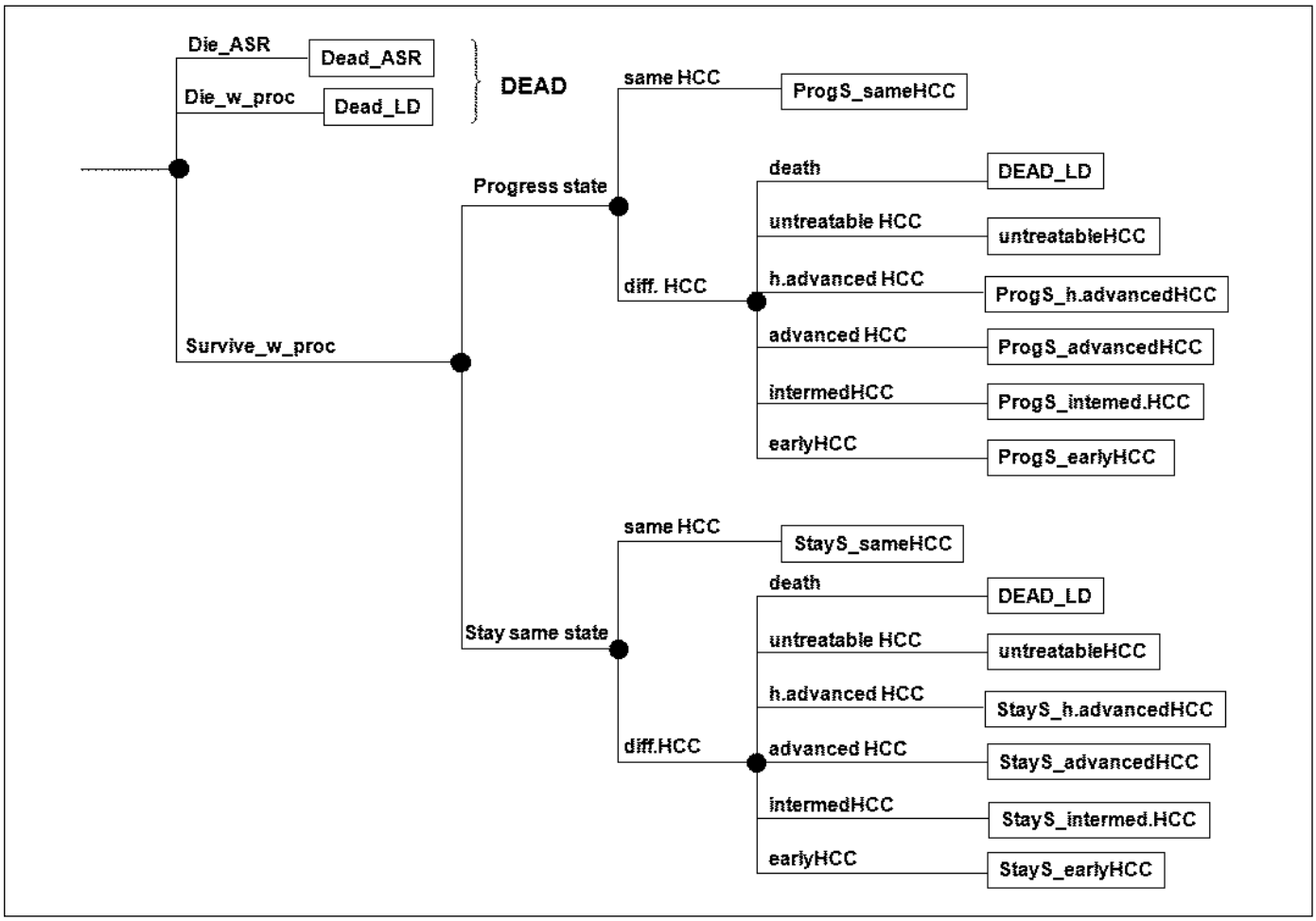

Fig. 4 Structure of sub-tree in one Markov cycle of our model. The first circular node, chance node, represents the probability of survival after therapeutic procedure ("survive_w_proc") and of death from age and sex ("die_ASR") or procedure-related death ("die_w_proc"). In the same cycle, underlying liver disease of survivors may progress from CH to compensated LC, or from compensated LC to decompensated LC ("progress state") or stay in the same condition ("same_state"). Patients may still remain in the same state of HCC after indicated therapeutic procedures ("same HCC"), or patients progressed to the advanced state or regressed to the improved one at the end of each cycle ("diff.HCC").

Simulation was performed on the TreeAge-Pro 2006 (TreeAge Software Inc.) with a one-month cycle and terminated when simulation reached 360 cycles (30 years) or the effectiveness of a cycle declined to be less than 0.001.

2.7 Validation of the Model

We validated the predictive performance of the model internally by comparing the survival curves using the actual data. As external validation, we also evaluated HR, LAT and TACE using the nationwide follow-up survey data. Cumulative survival rates were determined by patients registration data between 1992 and 2003 [8].

2.8 Statistical Analysis

The point estimation and 95% confidence intervals of the 1-year to 10-year survival rates were calculated using the Kaplan-Meier method and the Kalbfleisch and Prentice method [9]. The 95% CIs of survival curves predicted by the model were estimated by the simulation of a cohort with same size of the actual data without any censored cases.

3. Result

The monthly transition probability converted from the median transition period and the proportion of the next transitional states were basic data source of our model (Table 2). The median transition periods of initial treatment for early HCC states were 1859 days of HR and 1321 days of LAT, and those for non-early HCC were 484 days of LAT+TACE, 521 days of TACE and 508 days of HAIC, respectively. The corresponding periods of the treatment for recurrence were 460, 389, 390, 390, 297 days, respectively. The median transition period from one state to another in initial treatment declined progressively with the advance in the HCC state. The transition rates from initial treatment or recurrence one to progressed or regressed HCC states were also shown in Table 2. All of these figures were assigned in our Markov model.

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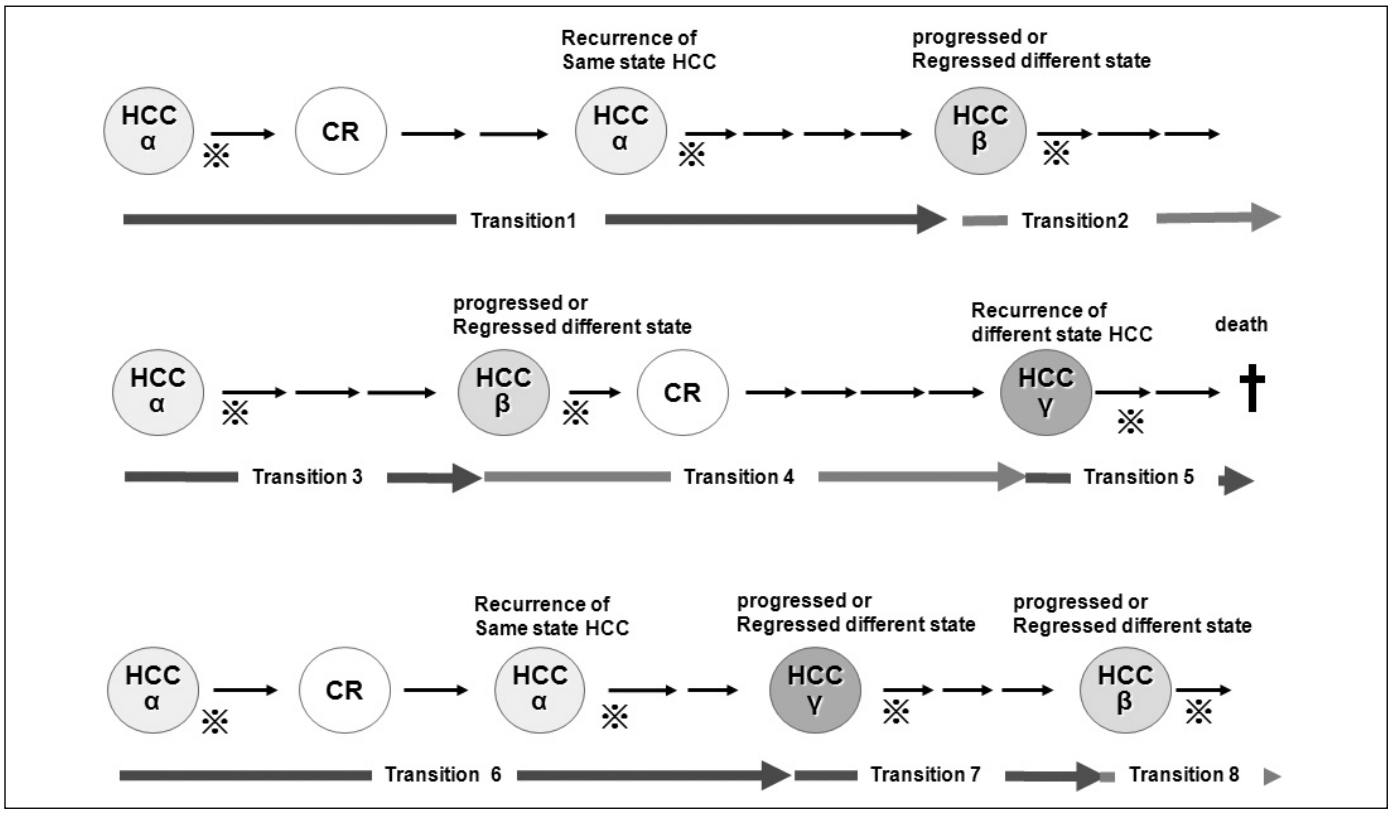

Fig. 5 Transition and length of transition period. Transition in our model was a change from one of the HCC states to the other irrespective of any treatment effect, such as complete remission or recurrence of the same state. The length of transition was obtained by the duration from the admission date for same HCC state to the admission date for different HCC state. For example, the transition periods for initial HCC α were estimated by the median periods of transition 1, 3 and 6 in the figure and two-thirds of the cases go to HCC β and one-third of the cases go to HCC γ. α, β and γ indicate the different HCC states, such as early, intermediate, advanced, etc. CR: complete remission. □ : treatment put into operation for each HCC state

Table 2 Transitional probabilities and the next transitional states

Stage	Treatment		Median (day)	Transitional probability (/month)	Next transitional state						
					Early		Intermediate	Advanced	Highly advanced	Terminal	Death
					HR	LAT					
Early HCC	HR	initial	1859	0.011	-	-	0.09	0.45	0.00	0.00	0.45
		recurrence	460	0.044	-	-	0.23	0.48	0.13	0.02	0.13
	LAT	initial	1321	0.016	-	-	0.32	0.37	0.22	0.02	0.18
		recurrence	389	0.052	-	-	0.30	0.42	0.10	0.06	0.12
Intermediate HCC	LAT+TACE	initial	484	0.042	0.03	0.20	-	0.60	0.06	0.04	0.07
		recurrence	390	0.052	0.04	0.19	-	0.57	0.09	0.01	0.10
Advanced HCC	TAC	initial	521	0.039	0.16	0.09	0.14	-	0.21	0.11	0.29
		recurrence	390	0.052	0.06	0.11	0.14	-	0.21	0.13	0.33
Highly advanced HCC	HAIC	initial	508	0.040	0.00	0.12	0.06	0.33	-	0.17	0.33
		recurrence	297	0.068	0.01	0.03	0.05	0.27	-	0.20	0.44
Terminal HCC			58	0.301	-	-	-	-	-	-	1.00

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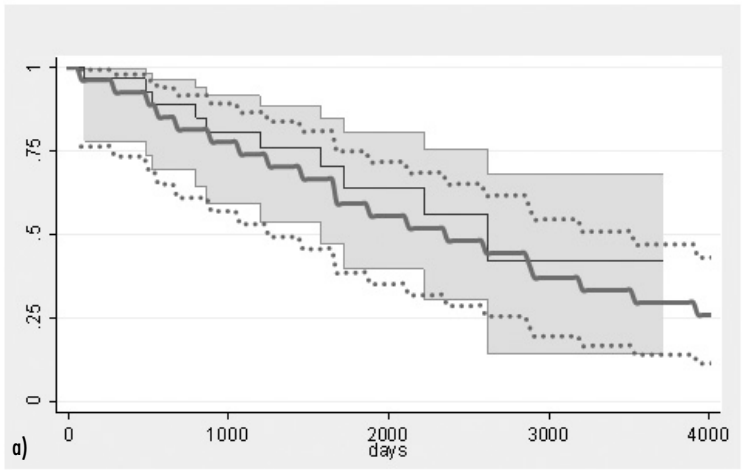
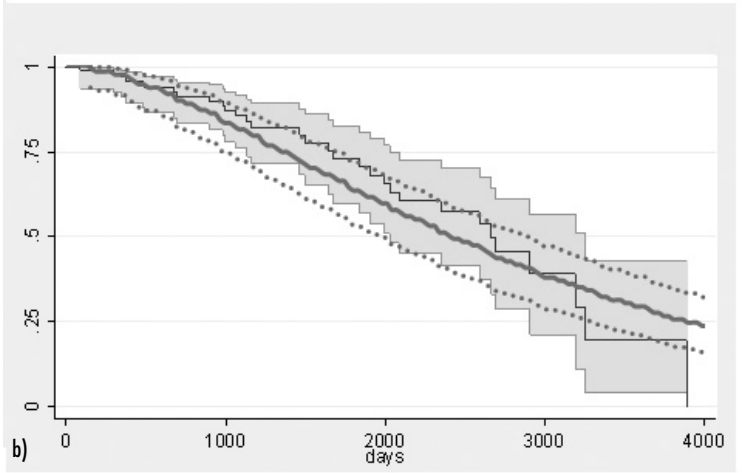
For internal validation, we compared the survival curves with 95% confidence interval (95% CI) bands between the Markov model and the KM method based on the original clinical data. Comparisons of their 1- to 10-year survival curve and rates of early HCC and non-early HCC were presented in Figures 6 and 7. These survival curves and the rates from the model for HR, LAT, TACE and HAIC exhibited substantial overlap within the 95% CIs. Representative 5-year survival comparisons between the KM curve and the Markov model were HR: 66% versus 60%, LAT: 74% versus 64%, LAT + TACE: 44% versus 38%, TACE: 34% vs. 31%, and HAIC: 24% vs. 26%, respectively. The difference between predicted survival rates and actual ones stayed within 10% in almost all treatment. The survival curves of HR were coarse and 95%CIs from the KM were fairly broad due to the small number of cases.

While the model may underestimate the survival for LAT + TACE (Fig. 7a), the survival curve was mostly sensitive to the transition probability of the initial treatment. If we adopt the transition rate at one year obtained from KM analysis of the cases, rather than the median transition period, to estimate the monthly transition probability after LAT + TACE treatment, it would be somewhat smaller (0.030) compared with the base data (0.042) and the predicted survival curve virtually overlapped the KM curve based on the actual data (Fig. 8).

On the other hand, predicted curves showed very analogous to those of external cohort. The predicted survival curve of HR by the Markov model overlapped with that for surveyed cases with solitary small (<2 cm in size) HCC with liver damage B as shown in Figure 9. Similarly, the survival curves of LAT by the Markov model overlapped with those of cases with solitary small HCC with liver damage A, and that the survival curve of TACE overlapped with HCC with liver damage A. These survival curves of the model and the nationwide survey were quite similar in their shapes (near linear decline in HR, sigmoidal decline in



Year	Actual Data		Model	
	Survival	95%CI	Base	95%CI
1	1.00	.	0.92	(0.74-0.98)
2	0.92	(0.72-0.98)	0.84	(0.61-0.92)
3	0.83	(0.62-0.93)	0.76	(0.53-0.87)
4	0.79	(0.56-0.91)	0.68	(0.49-0.84)
5	0.66	(0.41-0.83)	0.60	(0.39-0.75)
6	0.66	(0.41-0.83)	0.53	(0.32-0.69)
7	0.58	(0.31-0.77)	0.47	(0.29-0.65)
8	0.44	(0.15-0.70)	0.41	(0.23-0.58)
9	0.44	(0.15-0.70)	0.35	(0.17-0.51)
10	0.44	(0.15-0.70)	0.31	(0.14-0.47)



Year	Actual Data		Model	
	Survival	95%CI	Base	95%CI
1	0.98	(0.92-0.99)	0.96	(0.91-0.99)
2	0.92	(0.84-0.96)	0.90	(0.82-0.94)
3	0.86	(0.77-0.92)	0.81	(0.72-0.87)
4	0.83	(0.72-0.90)	0.73	(0.63-0.80)
5	0.74	(0.60-0.83)	0.64	(0.53-0.72)
6	0.61	(0.46-0.73)	0.55	(0.46-0.65)
7	0.58	(0.42-0.71)	0.47	(0.38-0.57)
8	0.39	(0.21-0.57)	0.40	(0.31-0.50)
9	0.20	(0.04-0.43)	0.34	(0.26-0.44)
10	0.20	(0.04-0.43)	0.29	(0.21-0.38)

Fig. 6 Survival curves of early HCC state (solitary and small tumor) predicted by the model and actual data. a) Initial treatment: hepatic resection; b) Initial treatment: LAT. The thick solid lines represent the predicted survival curves and dashed lines indicate their 95% confidence interval bands. The thin solid lines represent the KM survival curves from actual data and gray zones are their 95% confidence interval areas. The tables show the survival rates and their 95% confidence intervals at 1 to 10 years.

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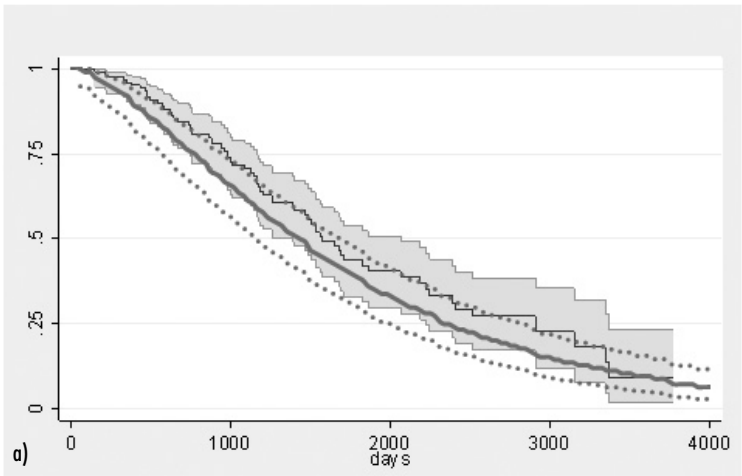
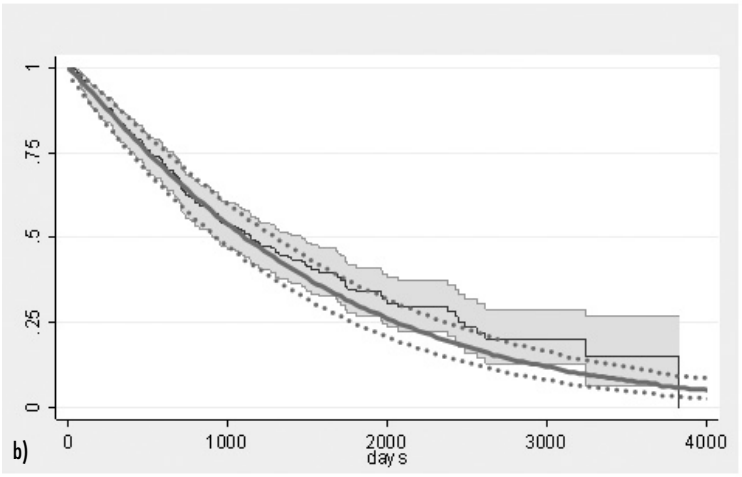
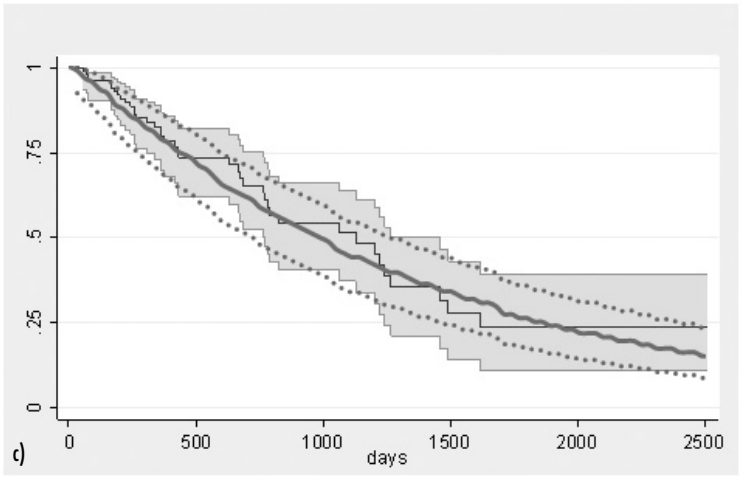


Year	Actual Data		Model	
	Survival	95%CI	Base	95%CI
1	0.96	(091-0.98)	0.91	(0.85-0.95)
2	0.84	(0.76-0.90)	0.77	(0.68-0.83)
3	0.71	(0.61-0.78)	0.62	(0.53-0.70)
4	0.58	(0.48-0.67)	0.49	(0.41-0.58)
5	0.44	(0.33-0.54)	0.38	(0.3-0.47)
6	0.37	(0.26-0.47)	0.30	(0.22-0.38)
7	0.27	(0.17-0.38)	0.22	(0.16-0.30)
8	0.23	(0.12-0.35)	0.17	(0.11-0.24)
9	0.18	(0.08-0.32)	0.13	(0.08-0.19)
10	0.09	(0.02-0.23)	0.09	(0.05-0.16)



Year	Actual Data		Model	
	Survival	95%CI	Base	95%CI
1	0.82	(0.77-0.86)	0.82	(0.76-0.86)
2	0.64	(0.57-0.69)	0.65	(0.59-0.71)
3	0.52	(0.45-0.58)	0.51	(0.45-0.58)
4	0.44	(0.36-0.50)	0.40	(0.34-0.46)
5	0.34	(0.27-0.41)	0.31	(0.25-0.36)
6	0.30	(0.22-0.37)	0.23	(0.18-0.29)
7	0.24	(0.16-0.32)	0.18	(0.13-0.23)
8	0.20	(0.13-0.29)	0.13	(0.09-0.18)
9	0.15	(0.06-0.27)	0.10	(0.07-0.14)
10	0.15	(0.06-0.27)	0.07	(0.05-0.11)



Year	Actual Data		Model	
	Survival	95%CI	Base	95%CI
1	0.80	(0.70-0.87)	0.79	(0.69-0.86)
2	0.65	(0.52-0.75)	0.60	(0.50-0.70)
3	0.51	(0.37-0.64)	0.46	(0.34-0.55)
4	0.32	(0.17-0.47)	0.35	(0.25-0.45)
5	0.24	(0.11-0.39)	0.26	(0.17-0.35)
6	0.24	(0.11-0.39)	0.19	(0.12-0.28)

Fig. 7 Survival curves of non-early HCC states predicted by the model and actual data. a) Initial treatment: combination of LAT and TACE; b) initial treatment: TACE; c) initial treatment: HAIC and systemic chemotherapy

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LAT and exponential decline in TACE) supporting the external validity of the Markov model.

4. Discussion

Great progress in the diagnosis and treatment for HCC over several decades brought improvement of its prognosis, however, the optimal management of HCC remains controversial. The reason is that the uncertainty to estimate prognosis by pretreatment factors including tumor characteristics [10] and high recurrence rate make it difficult to predict prognosis after various treatment procedures.

Our Markov model which assumed the treatment procedures as health states and incorporated two phase of transition probabilities predicted prognosis of various stage of HCC accurately. There have been several reports of Markov models predicting the natural course of HCC in studies for the cost-effectiveness of surveillance or therapy for HCC [11-16]. However, they had several different points compared with our model. Firstly, their models used single transitional probability after different treatment for HCC led to monotonous decline of the survival. As far as we surveyed using MEDLINE, all simulation models to estimate the prognosis after interventions for HCC had applied single transition probabilities in the whole course [11, 13, 16, 17]. Secondly, they used many variables obtained from several published studies which were different in study design and sample characteristics. Therefore, their variables incorporated in their models consisted of heterogeneous ones. Thirdly, the validations of models were insufficiently in almost all reports, and it was difficult to justify the appropriateness of their results.

On the contrary, our model using the Markov process had the following characteristics. Firstly, it was constructed based on hypothetical HCC states expressed by the concordant treatments and liver fibrotic states. We assumed the initial treatment would be selected by tumor characteristics and preserved liver function according to the treatment strategy of Yamaguchi University Hospital which was comparable to those of the Japanese clinical practice guidelines for HCC [18].

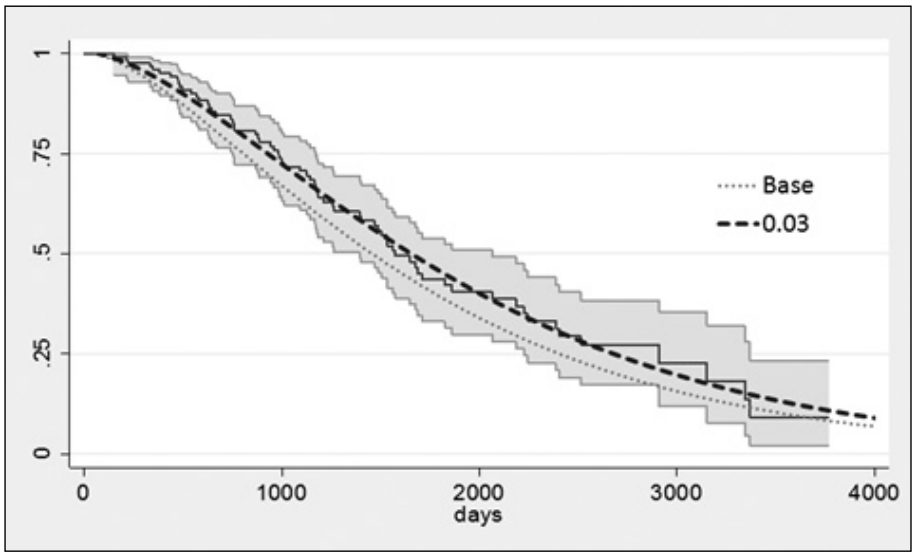

Fig. 8 Survival curves after adjustment of the transition probability from the initial LAT+TACE treatment. Dashed lines indicate the predicted survival curves and the solid line indicates the KM survival curves from actual data with gray zones representing the 95% confidence interval area.

Secondly, it used two-phase transition probabilities. It enabled us to evaluate the effect of the initial treatment correctly and project over a life-long course by recurrence. Frequent recurrences are common in HCV-related HCC and the effect of treatment tends to decline along with the recurrences. Moreover, the effect of initial treatments were found to be significantly and independently associated with patient survival as well as tumor characteristics. Those were determinant at the initial treatment [19]. Therefore, we grouped the model into the initial treatment state and the succeeding states for recurrences. Due to this separation, differences between the estimated transition periods from the initial treatment and those from treatments for recurrence in each HCC state was disclosed and more precise prediction of the prognosis could be expected.

Mathematical models have been proposed to predict prognosis, including the stochastic survival model using Cox regression model [20, 21], the hidden Markov [22] and the ordinary Markov model [23], and the discrete-event model [24]. Moreover, recent advances in computing have made it feasible to deal with more complicated methods that require time-consuming calculations, such as Bayesian estimation with Markov Chain Monte Carlo [25]. Among these models that can be applied to the clinical decision support, the Markov model has been characterized by its simplicity of model structure, its convenience in calculating the prognosis, and its responsible representation of many kinds of clinical problems [26]. Markov models are particularly useful in solving clinical problems that involve continuous risks that are ongoing over time. They are also useful for problems with repetitive events occurring with uncertain timing, which are difficult to deal with by a simple tree model. Modeling by conventional decision tree may require unrealistic or unjustified simplifying assumptions [27]. There is evidently trade-off in the relationship between the simplicity of the model and close reflection of the clinical course. The simpler the model structure is, the fewer the parameters in the model and the easier to understand, but the more risk of overestimation or underestimation. However, our Markov model enabled to allow incorporate the different treatment for the different stage of recurrence and hepatologists could accept the model because of its closeness to the clinical reality.

The predicted survival curves by the model were all consistent with the actual

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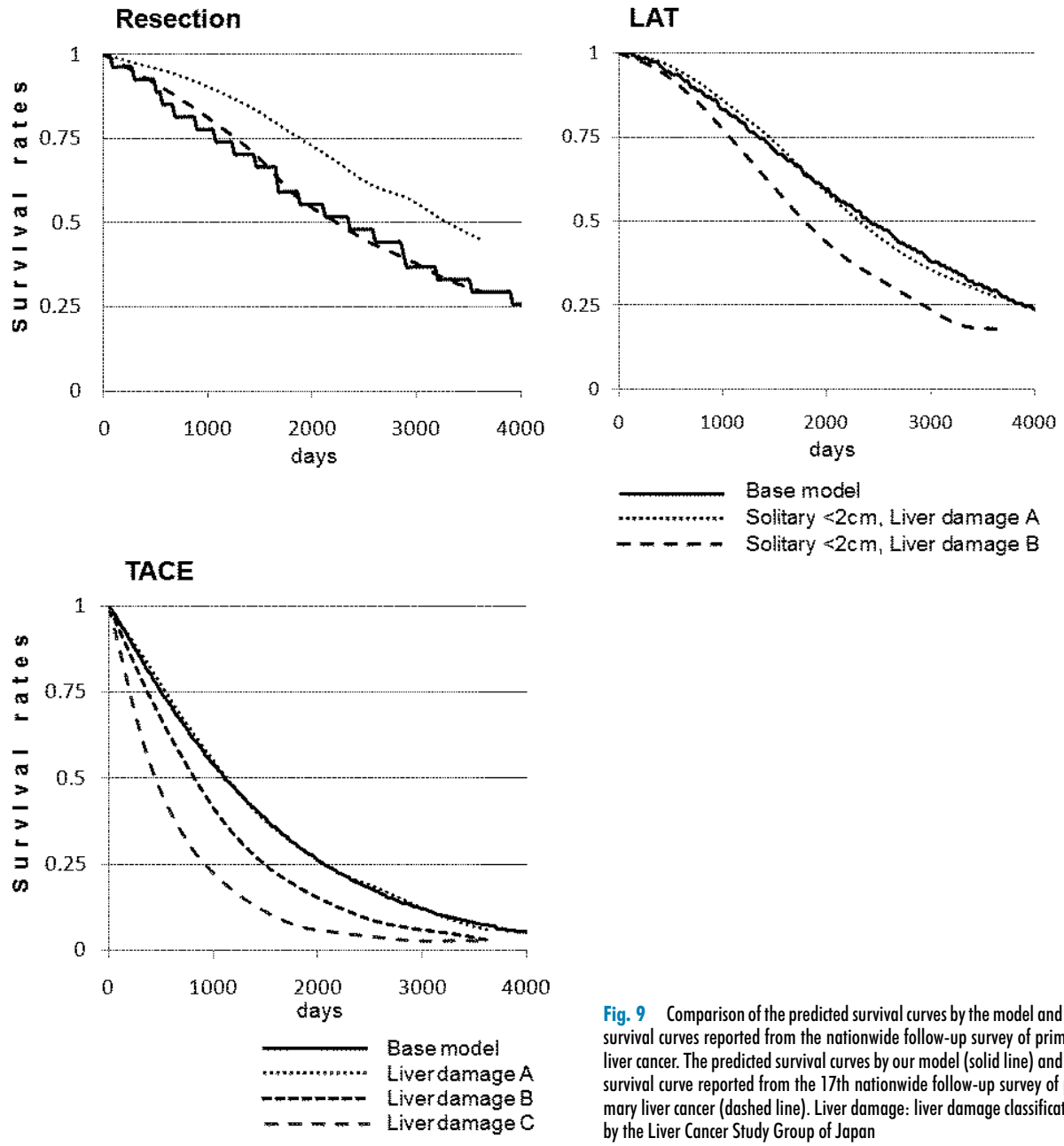

Fig. 9 Comparison of the predicted survival curves by the model and the survival curves reported from the nationwide follow-up survey of primary liver cancer. The predicted survival curves by our model (solid line) and the survival curve reported from the 17th nationwide follow-up survey of primary liver cancer (dashed line). Liver damage: liver damage classification by the Liver Cancer Study Group of Japan

curves except for LAT + TACE. The indication of this combination therapy was for oligo-nodular HCC, that is single segmental or sub-segmental lesion and distant small focal lesion. We considered these HCC states to be as intermediate states between the early HCC state and advanced one that optimal initial treatment was TACE. However, 60% of HCC cases treated by LAT + TACE as the initial treatment were treated by TACE at the next different state. It was possible that a proportion of this group might have originally been the same HCC states, which ought to be treated by TACE. Moreover, sensitivity analysis showed that the predicted curves were mostly affected by the initial transition probabilities. The estimated transition probabilities varied with the methods although we selected the median transition period for base case analysis rather than the person-year method, mean transition period or transition rate at a certain period. If the transition probability from the initial LAT + TACE was set at 0.03, which was obtained from the transition rate at one year from KM, and converted to the monthly probability, the predicted survival curve virtually overlapped with the KM curve based on the actual data. This result,

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therefore, indicated that estimation of the initial transition probabilities was crucial and we needed to know which method was best to accurately obtain figures of transition state. Considering time-dependent variables could be the limitation of simple Markov model

Comparing the predicted survival curves by model and those of the external survey data for HR, LAT and TACE, the shape of these curves were quite similar; although those from our actual data were superior to those of the external one.

Our model has the following limitations: Firstly, the model does not consider liver transplantation, while the number of living-donor liver transplantations (LDLT) from patients' relatives has increased in Japan [28]. Unfortunately, we had few cases of liver-transplantation, the criteria of liver-transplantation appear to be expanding and consensus has not been established. However, LDLT has increased worldwide and the successful results have been reported even in Japan [29]. Thus, we should incorporate the health state of liver transplantation in further trials if we can obtain sufficient data [30, 31].

Secondly, the cause of liver disease-related death included decompensated liver cirrhosis without HCC and terminal HCC state. The decompensated liver condition without HCC was considered as a consequent state after treatment for HCC and they frequently coexist. It is difficult to discriminate which is the direct cause, we did not distinguish between them.

Thirdly, we used retrospective data from three university hospitals, and combined them in one group. There were some differences in the prognosis among these facilities, especially HAIC. There might be some differences in selection criterion which affected sensitively on the estimation of survival curve. The prognosis after an initial treatment may be influenced by such criteria. Therefore, when we apply this model to cost-effectiveness and comparing the treatment, we need to adjust for the demographic factor, the HCC and the preserved liver state of the cases.

5. Conclusion

We constructed a Markov model that consisted of the first (initial) and the succeeding different treatment state. The survival curves from the model were close to those of the actual data, except for in the case of combination therapy with LAT and TACE, and were quite similar to those of external data.

Both internal and external validity of the developed Markov model for prediction of the prognosis after initial treatment for various HCC states were verified using actual and nation-wide survey data. The Markov model should be considered suitable for estimating the cost-effectiveness of screening and treatments for HCC.

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