Received:
11 November 2015

Revised:
31 March 2016

Accepted:
9 May 2016

<http://dx.doi.org/10.1259/bjr.20150945>

Cite this article as:

Okazaki E, Yamamoto A, Nishida N, Hamuro M, Ogino R, Hosono M, et al. Three-dimensional conformal radiotherapy for locally advanced hepatocellular carcinoma with portal vein tumour thrombosis: evaluating effectiveness of the model for end-stage liver disease (MELD) score compared with the Child–Pugh classification. *Br J Radiol* 2016; **89**: 20150945.

FULL PAPER

Three-dimensional conformal radiotherapy for locally advanced hepatocellular carcinoma with portal vein tumour thrombosis: evaluating effectiveness of the model for end-stage liver disease (MELD) score compared with the Child–Pugh classification

¹EIICHIRO OKAZAKI, MD, ¹AKIRA YAMAMOTO, MD, PhD, ²NORIFUMI NISHIDA, MD, PhD, ¹MASAO HAMURO, MD, PhD, ³RYO OGINO, MD, PhD, ¹MASAKO HOSONO, MD, PhD, ¹YASUHIKO SHIMATANI, MD, PhD, ¹SHINICHI TSUTSUMI, MD, PhD, ¹SHINICHI HAMAMOTO, MD, PhD, ¹ETSUJI SOHGAWA, MD, ¹ATSUSHI JOGO, MD, PhD and ¹YUKIO MIKI, MD, PhD

¹Department of Diagnostic and Interventional Radiology/Radiation Oncology, Osaka City University Graduate School of Medicine, Osaka, Japan

²Department of Radiology, Osaka Saiseikai Nakatsu Hospital, Osaka, Japan

³Department of Radiation Oncology, Tane General Hospital, Osaka, Japan

Address correspondence to: Mr Eiichiro Okazaki

E-mail: eiichiro.ok@gmail.com

Objective: The purpose of this study was to retrospectively evaluate the effectiveness of the model for end-stage liver disease (MELD) score compared with the Child–Pugh classification in patients who received three-dimensional conformal radiotherapy (3D CRT) for hepatocellular carcinoma (HCC) with portal vein tumour thrombosis (PVTT) by analyzing toxicity and prognostic factors.

Methods: 56 consecutive patients who had locally advanced HCC with PVTT treated by 3D CRT between September 2007 and April 2013 were retrospectively reviewed.

Results: The median survival time of all patients was 6.4 months. Receiver-operating characteristic (ROC) analysis identified MELD score = 7.5 [area under the curve (AUC) 0.81] and Child–Pugh score = 6.5 (AUC 0.86) as the best cut-off values for predicting the incidence of complications over Common Terminology Criteria for Adverse

Events grade 2. There was no significant difference in the discrimination power between the MELD score and the Child–Pugh score on comparison of the two ROC curves ($p = 0.17$). On multivariate analysis, age, MELD score and radiotherapy dose were significant prognostic factors for overall survival ($p = 0.021$, 0.038 and 0.006 , respectively). In contrast, the Child–Pugh classification, tumour response, PVTT response and the number of prior interventional radiologic treatments were not significant on multivariate analysis.

Conclusion: This study showed that the best MELD score cut-off value is 7.5 and that the MELD score is a better prognostic factor than the Child–Pugh classification in 3D CRT for HCC with PVTT.

Advances in knowledge: The MELD score is useful for predicting the risk of severe toxicities and the prognosis of patients treated with 3D CRT for PVTT.

Hepatocellular carcinoma (HCC) is one of the most common malignancies in adults.¹ Management of patients with HCC depends on the stage of their tumour. Portal vein tumour thrombosis (PVTT) is a common condition in patients with advanced HCC. PVTT may cause serious complications such as tumour spread, deterioration of liver function and portal vein hypertension, leading to intractable ascites, variceal rupture, hepatic encephalopathy or death.² The prognosis of HCC with PVTT is generally poor, with a median survival of several months.^{3–5} Moreover, in patients with large-vessel invasion, therapeutic

options are limited. In patients with PVTT, standard treatment has not been established and radiotherapy (RT) can be considered as an alternative treatment. RT has been infrequently used in the treatment of HCC owing to the risk of radiation-induced liver disease (RILD). However, recent advances in RT have enabled delivery of a higher dose to the tumour without serious complications.⁶

The Child–Pugh classification system has been widely used to predict the risk of death and complications in patients with cirrhosis. The Child–Pugh class B liver function,

extensive venous involvement and elevated tumour markers have been identified as poor prognostic factors in RT for HCC with PVTT.^{6–8} On the other hand, the model for end-stage liver disease (MELD) score is a mathematical model which is able to predict an individual's chance of survival after an elective transjugular intrahepatic portosystemic shunt, as reported by the Mayo Clinic.⁹ Recently, the MELD score has been widely used as an index of disease severity in various clinical situations such as liver transplantation, non-liver transplant surgery, variceal bleeding and hepatorenal syndrome, and it is reported to be more useful than the Child–Pugh classification.^{10–12} To the best of our knowledge, reports concerning the effectiveness of the MELD score in RT for liver disease have been rare¹³ and they have not compared the effectiveness of the MELD score with that of the conventional Child–Pugh classification.

The aim of this study was to retrospectively evaluate the effectiveness of the MELD score compared with the Child–Pugh classification in patients who underwent three-dimensional conformal radiotherapy (3D CRT) for HCC with PVTT by analyzing toxicity and prognostic factors.

METHODS AND MATERIALS

Patient population

The records of 56 consecutive patients who had locally advanced HCC with PVTT treated by 3D CRT between September 2007 and April 2013 at our institution were retrospectively reviewed. The diagnosis of HCC was based on the tissue proof, angiography or the typical imaging appearance on CT and/or MRI. PVTT was diagnosed by characteristic findings of ultrasonography, CT and/or MRI. Tumour invasion to the portal vein was classified according to the criteria of the Liver Cancer Study Group of Japan¹⁴ as portal tumour invasion involving second-order branches, first-order branches and the main trunk of the portal vein.

The eligibility criteria for this study were: performance status 0–2 on the Eastern Cooperative Oncology Group scale;¹⁵ liver function of Child–Pugh classification A or B; no extrahepatic metastasis; and no uncontrollable ascites.

This study was approved by the institutional review board of our institution and was conducted in accordance with the principles of the Declaration of Helsinki.

Table 1 lists the patient characteristics. The median age at diagnosis of PVTT was 71 years (range, 34–84 years). 11 patients had hepatitis B infection and 36 patients had hepatitis C. One patient had hepatitis B and C co-infection. In the patients infected with hepatitis C, 7 (19.4%) patients achieved sustained virologic response and 25 (69.4%) patients had continuous viral infection. In 4 (11.1%) patients, there were no available data about hepatitis C virus RNA. 10 patients were classified as having non-B non-C hepatitis (9 patients who were alcoholic and 1 unknown cause). 54 patients, about 96% of all patients, had received prior treatments before the current therapy. Operations were performed in 16 (29%) patients, catheter interventions such as transcatheter arterial infusion (TAI) chemotherapy and/or transarterial chemoembolization (TACE) were performed in 53 (95%) patients

Table 1. The demographic characteristics of the 56 consecutively reviewed patients in the present study

Characteristic	Number of patients
Age (years)	
69.1 ± 8.7 (median 71)	
Sex	
Male	48
Female	8
HBs Ag	
Negative	45
Positive	11
HCV Ab	
Negative	20
Positive	36
Child–Pugh classification	
A	39
B	17
Child–Pugh score: median (range)	6 (5–8)
MELD score: median (range)	8 (6–15)
Prior treatment	
None	2
Operation	16
TACE or/and TAI	52
RFA or/and PEIT	26
Tumour thrombi ^a	
Vp ₂	9
Vp ₃	24
Vp ₄	23

HBs Ag, hepatitis B virus surface antigen; HCV Ab, hepatitis C virus antibody; MELD, model for end-stage liver disease; PEIT, percutaneous ethanol injection therapy; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TAI, transcatheter arterial infusion; Vp₂, second order branches of the portal vein; Vp₃, first order branches of the portal vein; Vp₄, main trunk of the portal vein.

^aClassification according to the Liver Cancer Study Group of Japan criteria.

and radiofrequency ablation and/or percutaneous ethanol injection therapy was performed in 26 (46%) patients.

Radiotherapy

Patients were placed in the supine position with both arms raised above the head and with the head in a natural position. Craniocaudal margins were determined to compensate for the respiration-related movement of the target volume, which was assessed by fluoroscopic visualization of the diaphragmatic motion. The gross tumour volume (GTV) was defined as the tumour thrombosis visualized on the contrast-enhanced CT images near the primary liver lesions. The clinical target volume (CTV) was defined as the GTV plus 1 cm. The planning target

volume included CTV GTV plus 0.5 cm for daily setup margin and 0.5–2.0 cm in the craniocaudal dimension to account for respiratory motion. Normal liver was defined as the whole liver volume minus the CTVs. Radiation therapy was given using a 3D conformal technique. Each treatment plan was evaluated with a cumulative dose–volume histogram. 3D CRT was planned to ensure that the normal liver volume irradiated with 30 Gy did not exceed 30% for the purpose of preventing RILD.¹⁶

The treatments were delivered with a PRIMUS (Siemens, Erlangen, Germany) or a Synergy (Elekta, Stockholm, Sweden) linear accelerator. A daily dose of 2.0 Gy was administered through two to four ports using a 6- or 10-MV linear accelerator, at five fractions per week, to deliver a total median dose of 50 Gy. A total radiation dose of 22–50 Gy (median, 50 Gy) was delivered (22 Gy in 1 patient, 26 Gy in 1 patient, 34 Gy in 1 patient, 40 Gy in 5 patients, 42 Gy in 1 patient, 46 Gy in 2 patients, 48 Gy in 1 patient and 50 Gy in 44 patients). 2 patients could not complete the course of RT because of worsening of their general condition, and 10 patients received a dose <50 Gy because of poor general condition, hepatorenal failure or dose constraint of normal liver. During treatment, the patients were monitored weekly with physical examinations and blood chemistry evaluations.

In this study, 37 patients received combined therapy with interventions such as TAI and TACE and RT. The typical chemotherapeutic agents used for TAI and TACE were cisplatin, doxorubicin, mitomycin C, epirubicin and miriplatin. Combined TAI or TACE was performed within 1–3 weeks before the start of RT.

Response evaluation and radiotherapy toxicity

Treatment response was evaluated on serial CT images obtained 4–8 weeks after the completion of RT. Response was based on the change in tumour size within the treatment volume, using the response evaluation criteria in solid tumours 1.1 criteria.¹⁷ Complete disappearance of the tumour was defined as a complete response (CR), a decrease of $\geq 30\%$ in tumour size was defined as a partial response (PR), a decrease of $<30\%$ or an increase of $<20\%$ was defined as stable disease (SD) and an increase of $\geq 20\%$ was defined as progressive disease (PD). The product of the largest perpendicular diameters of the PVTT was also calculated and compared with the basal value recorded. Complete disappearance of the PVTT was defined as CR, a decrease of $\geq 50\%$ in thrombus size was defined as PR, a decrease of $<50\%$ or an increase of $<25\%$ was defined as SD and an increase of $\geq 25\%$ was defined as PD.

RT toxicities were documented using the National Cancer Institute's Common Terminology Criteria for Adverse Events v. 4.0. All patients were also evaluated for RILD, defined as either a minimum twofold increase in the anicteric elevation of alkaline phosphatase levels and non-malignant ascites or a minimum fivefold increase in transaminase levels over the normal upper limit or of pre-treatment levels in the absence of documented PD.¹⁸

Statistical analysis

Pearson's correlation coefficients were calculated to assess the strength of the linear relationship between the MELD and

Child–Pugh scores. Coordinate points of a receiver-operating characteristic (ROC) curve were used to identify significant points of the MELD score and Child–Pugh classification as predictors of severe toxicities and survival (at 3, 6 and 12 months) after 3D CRT. Survival time from the point at which RT began was calculated by the Kaplan–Meier method. The prognostic values of variables were analyzed by the log rank test. The independence of prognostic factors for survival was evaluated by a multivariate Cox regression model using a stepwise selection procedure. Comparison of the characteristics was performed using the *t*-test. Statistical analyses were performed using JMP software v. 9.0.2 (SAS Institute, Cary, NC) and R environment v. 3.2.2 (R Foundation) available from <http://www.r-project.org>. A *p*-value of <0.05 was considered significant. ROC curve analysis and comparisons between ROC curves was performed using the pROC, a package for R that contains a set of tools comparing ROC curves with statistical tests.¹⁹ Bonferroni correction was used to adjust for multiple comparisons.

RESULTS

The median follow-up time and the median survival time of all patients were 5.3 and 6.4 months, respectively. 46 (82%) patients died during follow-up. In 50 patients, the responses of the tumour and PVTT could be assessed on radiologic imaging before and after RT. Tumour responses were: CR in 0 patients, PR in 11 (22.0%) patients, SD in 22 (44.0%) patients and PD in 17 (34.0%) patients. The response rate (CR + PR) was 22.0%, and the progression-free rate (CR + PR + SD) was 66.0%. PVTT responses were: CR in 1 (2.0%) patient, PR in 12 (24.0%) patients, SD in 19 (38.0%) and PD in 18 (36.0%) patients. The response rate (CR + PR) was 26.0%, and the progression-free rate (CR + PR + SD) was 64.0%.

The median MELD and Child–Pugh scores were 8 (range, 6–15) and 6 (range, 5–8), respectively. Pearson's test demonstrated a significant correlation between the MELD score and the Child–Pugh score ($r = 0.62$, p -value < 0.001).

Table 2. Radiation toxicity ($n = 56$)

Toxicity	Grade ^a		
	2	3	4
Hepatic			
Transaminase	3	2	–
Bilirubin	8	4	–
Albumin	8	–	–
Alkaline phosphatase	6	–	–
Haematologic			
Anaemia	9	–	–
Leukopenia	12	7	–
Thrombocytopenia	12	6	1
Gastrointestinal	17	–	–

^aToxicity was graded according to the Common Terminology Criteria for Adverse Events (v. n 4.0).

Figure 1. The receiver-operating characteristic curves of the model for end-stage liver disease (MELD) and Child-Pugh scores for predicting the incidence of severe acute toxicities after radiotherapy.

Toxicity

The toxicity of 3D CRT is summarized in Table 2. Gastrointestinal toxicities included nausea, vomiting, loss of appetite, diarrhoea, abdominal distension and gastritis. 12 patients had grade 2 loss of appetite and/or nausea, 3 patients had grade 2 diarrhoea, 1 patient had grade 2 abdominal distension and 1 patient had grade 2 gastritis. No patient had radiation-related gastrointestinal bleeding. RILD was not seen in this study. There were no RT-related deaths.

ROC analysis identified MELD score = 7.5 [area under the curve 0.81; 95% confidence interval (CI) = 0.69–0.93; sensitivity = 92.6%; and specificity = 60.0%] and Child-Pugh score = 6.5 (area under the curve 0.86; 95% CI = 0.75–0.97; sensitivity = 73.3%; and specificity = 85.4%) as the best cut-off values for predicting the incidence of complications over grade 2 with Common Terminology Criteria for Adverse Events (Figure 1). Severe toxicities were more frequently seen in patients with MELD

Figure 3. Kaplan-Meier survival curves according to the model for end-stage liver disease (MELD) score with a cut-off value of 7.5 ($p = 0.0014$).

score ≥ 7.5 or Child-Pugh score ≥ 6.5 (p -value < 0.001 for both). There was no significant difference in the discrimination power between the MELD score and the Child-Pugh score on comparison of the two ROC curves (p -value = 0.17).

Survival and prognostic factors

The discrimination power on ROC analysis of the MELD score for 3-month survival was 0.66 (95% CI = 0.48–0.85, best cut-off value = 10.5) and that of the Child-Pugh score was 0.76 (95% CI = 0.60–0.92, best cut-off value = 6.5) (Figure 2). There was no significant difference between the two groups (p -value = 0.29). Similarly, the discrimination powers of the MELD score for 6- and 12-month survivals (6-month survival: 0.67, 95% CI = 0.53–0.81; 12-month survival: 0.62, 95% CI = 0.47–0.77, respectively) were not significantly different from those of the Child-Pugh score (6-month survival: 0.69, 95% CI = 0.56–0.82, p -value = 0.66; 12-month survival: 0.60, 95% CI = 0.46–0.75, p -value = 0.98, respectively). The cut-off values of the MELD score were 10.5 for 3-month survival and 7.5 for 6- and 12-month survivals.

Figure 2. The receiver-operating characteristic curves of the model for end-stage liver disease (MELD) and Child-Pugh scores for predicting survival at 3 months after radiotherapy.

Figure 4. Kaplan-Meier survival curves according to the model for end-stage liver disease (MELD) score with a cut-off value of 10.5 ($p = 0.032$).

Table 3. Prognostic factors of patients treated with radiotherapy (RT)

Variables	Number of patients	Univariate analysis		Multivariate analysis	
		MS	<i>p</i> -values	<i>p</i> -values	HR (95% CI)
Age (years)					
<70	26	6.4	0.15	0.021	2.30 (1.13–4.68)
≥70	30	5.2			
Sex					
Male	48	5.4	0.49		
Female	8	13.5			
HBs Ag					
Negative	45	6.4	0.56		
Positive	11	5.4			
HCV Ab					
Negative	20	9.0	0.55		
Positive	36	5.1			
Child–Pugh classification					
A	39	9.0	0.085	NS	
B	17	3.0			
MELD score					
<7.5	25	10.6	0.0014	0.038	2.08 (1.04–4.14)
≥7.5	29	4.3			
Unknown	2				
Tumour thrombi ^a					
Vp ₂ + Vp ₃	33	6.8	0.67		
Vp ₄	23	3.7			
Number of TACE and TAI treatments					
<3	30	8.8	0.84		
≥3	26	4.9			
Number of RFA and PEIT treatments					
0	30	5.2	0.66		
≥1	26	8.9			
Combined TAI					
RT alone	19	11.2	0.55		
Combined TAI	37	5.2			
RT dose					
<50 Gy	12	3.2	0.0038	0.0064	0.33 (0.14–0.73)
= 50 Gy	44	9.0			
Tumour response to RT					
CR + PR + SD	33	9.1	0.065	NS	
PD	17	4.1			
PVTT response to RT					
CR + PR + SD	32	10.6	0.16	NS	
PD	18	5.4			

CI, confidence interval; CR, complete response; HBs Ag, hepatitis B virus surface antigen; HCV Ab, hepatitis C virus antibody; HR, hazard ratio; MELD, model for end-stage liver disease; MS, median survival (months); NS, not significant; PD, progressive disease; PEIT, percutaneous ethanol injection therapy; PR, partial response; PVTT, portal vein tumour thrombosis; RFA, radiofrequency ablation; SD, stable disease; TACE, transarterial chemoembolization; TAI, transcatheter arterial infusion Vp₂, second order branches of the portal vein; Vp₃, first order branches of the portal vein; Vp₄, main trunk of the portal vein.

^aClassification according to the Liver Cancer Study Group of Japan criteria.

Table 4. Comparison of two groups divided by a model for end-stage liver disease (MELD) score cut-off value of 7.5 median (range)

	Age (years)	RT dose (Gy)	PTV volume (ml)	Normal liver volume (ml)	Mean liver dose (Gy)
MELD < 7.5	70 (34–79)	50 (40–50)	174 (97–538)	1362 (908–1991)	17.9 (12.9–24.3)
MELD ≥ 7.5	71 (53–84)	50 (22–50)	172 (67–422)	1297 (916–2322)	18.1 (9.6–23.5)

PTV, planning target volume; RT, radiotherapy.

Using the log rank test and Bonferroni correction, the survival curve with the cut-off value of the MELD score was significantly different at MELD score = 7.5 (p -value = 0.0014), but it was not significant at MELD score = 10.5 (p -value = 0.032) (Figures 3 and 4).

Univariate and multivariate analyses are shown in Table 3. On multivariate analysis, age, MELD score and RT dose were significant prognostic factors for overall survival, while the Child–Pugh classification was not significant. Tumour response, PVTT response and the number of interventional radiologic (IR) treatments such as TAI, TACE, radiofrequency ablation and percutaneous ethanol injection therapy also did not affect the overall survival on multivariate analysis.

Differences in clinical characteristics between the two groups divided by a MELD score cut-off value of 7.5 were assessed (Table 4). There were no significant differences in age, RT dose, planning target volume, normal liver volume and mean liver dose (p -value = 0.98, 0.19, 0.48, 0.98 and 0.86, respectively).

DISCUSSION

This study showed that the best cut-off point of the MELD score for predicting severe acute toxicity and survival was 7.5, and the MELD score was a better prognostic factor than the Child–Pugh classification in 3D CRT for HCC with PVTT. Historically, the Child–Pugh classification system, first used to evaluate liver function in patients with cirrhosis, has been widely used to predict the risk of death and complications, and it has also been used in RT. On the other hand, the Child–Pugh classification has several limitations.²⁰ The five components of the Child–Pugh classification were selected empirically and each variable was given the same weight. Furthermore, two variables (ascites and encephalopathy) are based on subjective assessment and can be altered by therapy. The MELD score is a scoring system that relies on three simple objective laboratory values [serum total bilirubin level, international normalized ratio and serum creatinine level] selected by statistical analysis and each variable is weighted by its specific effect on prognosis.²¹ This scoring system has been demonstrated to be a reliable predictive tool for all patients with advanced liver disease, regardless of the underlying aetiology.^{22,23} In this study, the ability of the MELD score was compared with that of the Child–Pugh score to predict the risk of mortality and toxicity in patients with cirrhosis following RT. To the best of our knowledge, this is the first report to assess the effectiveness of the MELD score compared with the Child–Pugh classification in RT.

The MELD score has a limitation in that there is no clearly defined cut-off value. Different cut-off values of the MELD score must be determined for different situations. Two cut-off values (7.5 and 10.5) determined using ROC curve analyses for toxicity

and survival were compared, and a MELD score of 7.5 was the better cut-off value for predicting toxicity and survival after RT. There have been several reports using the MELD score as a prognostic variable in various clinical settings and populations. Using the MELD score for predicting 3-month mortality among patients awaiting liver transplantation, the mortality rate was 1.9% for patients with a MELD score <9, and the mortality rate was 71% for patients with a MELD score ≥40.²⁴ The best outcomes with transjugular intrahepatic portosystemic shunt occurred among patients with a MELD score <14.⁹ In the management of hepatorenal syndrome, a MELD score ≥20 was associated with significantly shorter transplantation-free survival than a lower MELD score.²⁵ Comparing these reports, the cut-off value of the MELD score of 7.5 in the present study is lower. One plausible reason for this is that hepatic irradiation can be regarded as toxic, especially for patients with cirrhosis. Another reason is that the present study targeted patients who had PVTT, some of whom received IR treatments several times before RT. PVTT can be considered as a serious condition with a very poor prognosis, and it may have caused the cut-off value in the present study to be lower than that in the previous studies.

Multivariate analysis demonstrated that the MELD score is the significant prognostic factor for overall survival (p -value = 0.038). In contrast, the Child–Pugh classification was not significant. It was also shown that the MELD score and the Child–Pugh classification were the significant factors for predicting severe toxicity following RT (p -value < 0.001 for both). There was no significant difference in the discrimination power between the two scores for predicting severe toxicity (p -value = 0.17). These results indicated that the MELD score may be a better prognostic factor for survival and have a similar discrimination power for predicting severe toxicities in RT compared with the Child–Pugh classification. Previous studies showed that the MELD score was more useful than the Child–Pugh classification in various situations in patients with cirrhosis.^{10–12} The present results suggest that the MELD score is also useful in RT, as previously shown. On the other hand, the Child–Pugh classification is a widely accepted, simple and intuitive scoring system, and it can remain a major tool for the management of patients with cirrhosis. Therefore, it appears that the MELD score and the Child–Pugh classification complement each other and provide a more accurate and beneficial assessment in patients with cirrhosis.

In the present study, the median survival time was 6.4 months, and this result may be slightly worse than that in previous reports.^{6,7,26–30} The following are the possible reasons for this result. First, most patients in this study had a longer history of treatment and had received several prior treatments, such as surgery and IR therapy, before RT. Second, the present study population consisted of elderly patients (median age, 71 years).

The other reason is that the patients included were those who had received an RT dose <50 Gy. Age and RT dose were found to be significant prognostic factors for survival on multivariate analysis in the present study. When limited to patients who had received 50 Gy, the median survival time was 9.0 months, which is comparable with that in previous reports. On the other hand, there may have been a bias related to RT dose. In the present study, RT dose was decreased for poor general condition, hepatorenal failure or dose constraint of the normal liver. Therefore, it is necessary to be careful when interpreting these results. Even though several factors may have affected the survival, one must consider the impact of the present finding that the median survival time of patients with a higher MELD score (≥ 7.5) was 4.3 months. The median survival time of patients with a higher MELD score (≥ 7.5) is not very different from that of patients with untreated PVTT. Although there was no significant correlation between the number of prior IR treatments and survival, prior IR treatments may be a potential cause of deterioration of liver function. It may be argued that patients with higher MELD scores may not benefit from aggressive RT, and other therapeutic options that provide symptom relief and pain management should be offered.

Combining IR treatments with 3D CRT did not prolong overall survival compared with 3D CRT alone in the present study. Most of the patients received TAI as combination therapy; therefore, it can be considered that TAI with 3D CRT did not improve the outcomes of patients with PVTT. The liver function of patients treated with combined therapy was significantly different from that of patients treated with 3D CRT alone [median MELD score 8.0 (range, 8.11–9.89) vs 7.0 (6.51–8.94) (p -value = 0.03) and median Child–Pugh score 6.0 (range, 5.84–6.65) vs 5.0 (5.25–5.91) (p -value = 0.06)]. Rim et al²⁹ showed a similar result and mentioned that the patients who received hepatic artery infusion might have had a worse clinical condition, and there might have been selective bias.

On univariate analysis, patients who achieved good tumour and PVTT control (CR + PR + SD) had longer survival than patients with PD. However, there was no significant difference in survival between responders and non-responders on multivariate analysis. Most previous studies have shown that patients with an objective response to RT for PVTT had longer survival than patients with no response.^{16,30–32} In the present study, RT dose was a significant prognostic factor on multivariate analysis. Although there was no significant difference in the RT dose between responders and non-responders (data not shown), the RT dose may have affected the tumour and PVTT responses in the multivariate analysis.

The present study had several limitations. First, this was a retrospective study performed at a single centre, and the sample size was small. Second, this study consisted of many patients who had a long history of HCC. Therefore, modification by previous treatment cannot be ignored. Third, it is known that an increase in the dose of RT has an important influence on the treatment outcome of HCC.²⁹ In the present study, RT was administered with a median total dose of 50 Gy; however, this dose may not be adequate to treat HCC with PVTT. Advanced techniques such as intensity-modulated RT, stereotactic body RT and proton therapy need to be considered as possible treatments to enable delivery of higher doses without added toxicity. Moreover, there are other scoring systems for patients with cirrhosis, such as the Assessment for Retreatment with TACE score,³³ to predict outcomes of liver disease. Further studies will be needed to evaluate these scoring systems in RT.

In conclusion, the MELD score is useful for predicting the risk of severe toxicity following RT. The best cut-off value of the MELD score is 7.5, and the MELD score is a better prognostic factor than the Child–Pugh classification in 3D CRT for HCC with PVTT.

REFERENCES

1. El-Serag HB. Hepatocellular carcinoma. *N Engl J Med* 2011; **365**: 1118–27. doi: <http://dx.doi.org/10.1056/NEJMra1001683>
2. Pirisi M, Avellini C, Fabris C, Scott C, Bardus P, Soardo G, et al. Portal vein thrombosis in hepatocellular carcinoma: age and sex distribution in an autopsy study. *J Cancer Res Clin Oncol* 1998; **124**: 397–400. doi: <http://dx.doi.org/10.1007/s004320050189>
3. Llovet JM, Bustamante J, Castells A, Vilana R, Ayuso Mdel C, Sala M, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology* 1999; **29**: 62–7. doi: <http://dx.doi.org/10.1002/hep.510290145>
4. Cheong JY, Lee KM, Cho SW, Won JH, Kim JK, Wang HJ, et al. Survival benefits of intra-arterial infusion chemotherapy in patients with advanced hepatocellular carcinoma with portal vein tumor thrombosis. *Hepatol Res* 2005; **32**: 127–33. doi: <http://dx.doi.org/10.1016/j.hepres.2005.01.015>
5. Takizawa D, Kakizaki S, Sohara N, Sato K, Takagi H, Arai H, et al. Hepatocellular carcinoma with portal vein tumor thrombosis: clinical characteristics, prognosis, and patient survival analysis. *Dig Dis Sci* 2007; **52**: 3290–5. doi: <http://dx.doi.org/10.1007/s10620-007-9808-2>
6. Klein J, Dawson LA. Hepatocellular carcinoma radiation therapy: review of evidence and future opportunities. *Int J Radiat Oncol Biol Phys* 2013; **87**: 22–32. doi: <http://dx.doi.org/10.1016/j.ijrobp.2012.08.043>
7. Tanaka Y, Nakazawa T, Komori S, Hidaka H, Okuwaki Y, Takada J, et al. Radiotherapy for patients with unresectable advanced hepatocellular carcinoma with invasion to intra-hepatic large vessels: efficacy and outcomes. *J Gastroenterol Hepatol* 2014; **29**: 352–7. doi: <http://dx.doi.org/10.1111/jgh.12333>
8. Yoon SM, Lim YS, Won HJ, Kim JH, Kim KM, Lee HC, et al. Radiotherapy plus transarterial chemoembolization for hepatocellular carcinoma invading the portal vein: long-term patient outcomes. *Int J Radiat Oncol Biol Phys* 2012; **82**: 2004–11. doi: <http://dx.doi.org/10.1016/j.ijrobp.2011.03.019>
9. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing

- transjugular intrahepatic portosystemic shunts. *Hepatology* 2000; **31**: 864–71. doi: <http://dx.doi.org/10.1053/he.2000.5852>
10. Klein KB, Stafinski TD, Menon D. Predicting survival after liver transplantation based on pre-transplant MELD score: a systematic review of the literature. *PLoS One* 2013; **8**: e80661. doi: <http://dx.doi.org/10.1371/journal.pone.0080661>
 11. Al Sibae MR, Cappell MS. Accuracy of MELD scores in predicting mortality in decompensated cirrhosis from variceal bleeding, hepatorenal syndrome, alcoholic hepatitis, or acute liver failure as well as mortality after non-transplant surgery or TIPS. *Dig Dis Sci* 2011; **56**: 977–87. doi: <http://dx.doi.org/10.1007/s10620-010-1390-3>
 12. Northup PG, Wanamaker RC, Lee VD, Adams RB, Berg CL. Model for End-Stage Liver Disease (MELD) predicts nontransplant surgical mortality in patients with cirrhosis. *Ann Surg* 2005; **242**: 244–51. doi: <http://dx.doi.org/10.1097/01.sla.0000171327.29262.e0>
 13. Cupino AC, Hair CD, Angle JF, Caldwell SH, Rich TA, Berg CL, et al. Does external beam radiation therapy improve survival following transarterial chemoembolization for unresectable hepatocellular carcinoma? *Gastrointest Cancer Res* 2012; **5**: 13–7.
 14. Japan LCSG. *The general rules for the clinical and pathological study of primary liver cancer*, 5th edn. Tokyo: Kanehara; 2009.
 15. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649–55. doi: <http://dx.doi.org/10.1097/00000421-198212000-00014>
 16. Yamada K, Izaki K, Sugimoto K, Mayahara H, Morita Y, Yoden E, et al. Prospective trial of combined transcatheter arterial chemoembolization and three-dimensional conformal radiotherapy for portal vein tumor thrombus in patients with unresectable hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2003; **57**: 113–9. doi: [http://dx.doi.org/10.1016/S0360-3016\(03\)00434-6](http://dx.doi.org/10.1016/S0360-3016(03)00434-6)
 17. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228–47. doi: <http://dx.doi.org/10.1016/j.ejca.2008.10.026>
 18. Lawrence TS, Robertson JM, Anscher MS, Jirtle RL, Ensminger WD, Fajardo LF. Hepatic toxicity resulting from cancer treatment. *Int J Radiat Oncol Biol Phys* 1995; **31**: 1237–48. doi: [http://dx.doi.org/10.1016/0360-3016\(94\)00418-K](http://dx.doi.org/10.1016/0360-3016(94)00418-K)
 19. Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez JC, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics* 2011; **12**: 77. doi: <http://dx.doi.org/10.1186/1471-2105-12-77>
 20. Durand F, Valla D. Assessment of the prognosis of cirrhosis: Child–Pugh versus MELD. *J Hepatol* 2005; **42**(Suppl. 1): S100–7. doi: <http://dx.doi.org/10.1016/j.jhep.2004.11.015>
 21. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**: 464–70. doi: <http://dx.doi.org/10.1053/jhep.2001.22172>
 22. Said A, Williams J, Holden J, Remington P, Gangnon R, Musat A, et al. Model for end stage liver disease score predicts mortality across a broad spectrum of liver disease. *J Hepatol* 2004; **40**: 897–903. doi: <http://dx.doi.org/10.1016/j.jhep.2004.02.010>
 23. Zhang J, Ye L, Zhang J, Lin M, He S, Mao X, et al. MELD scores and Child–Pugh classifications predict the outcomes of ERCP in cirrhotic patients with choledocholithiasis: a retrospective cohort study. *Medicine (Baltimore)* 2015; **94**: e433. doi: <http://dx.doi.org/10.1097/MD.0000000000000433>
 24. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al; United Network for Organ Sharing Liver Disease Severity Score Committee. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003; **124**: 91–6. doi: <http://dx.doi.org/10.1053/gast.2003.50016>
 25. Alessandria C, Ozdogan O, Guevara M, Restuccia T, Jiménez W, Arroyo V, et al. MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. *Hepatology* 2005; **41**: 1282–9. doi: <http://dx.doi.org/10.1002/hep.20687>
 26. Hou JZ, Zeng ZC, Zhang JY, Fan J, Zhou J, Zeng MS. Influence of tumor thrombus location on the outcome of external-beam radiation therapy in advanced hepatocellular carcinoma with macrovascular invasion. *Int J Radiat Oncol Biol Phys* 2012; **84**: 362–8. doi: <http://dx.doi.org/10.1016/j.ijrobp.2011.12.024>
 27. Kim JY, Chung SM, Choi BO, Kay CS. Hepatocellular carcinoma with portal vein tumor thrombosis: improved treatment outcomes with external beam radiation therapy. *Hepatol Res* 2011; **41**: 813–24. doi: <http://dx.doi.org/10.1111/j.1872-034X.2011.00826.x>
 28. Lin CS, Jen YM, Chiu SY, Hwang JM, Chao HL, Lin HY, et al. Treatment of portal vein tumor thrombosis of hepatoma patients with either stereotactic radiotherapy or three-dimensional conformal radiotherapy. *Jpn J Clin Oncol* 2006; **36**: 212–7. doi: <http://dx.doi.org/10.1093/jjco/hy1006>
 29. Kim CH, Yang DS, Park YJ, Yoon WS, Lee JA, Kim CY. Effectiveness of high-dose three-dimensional conformal radiotherapy in hepatocellular carcinoma with portal vein thrombosis. *Jpn J Clin Oncol* 2012; **42**: 721–9. doi: <http://dx.doi.org/10.1093/jjco/hys082>
 30. Zeng ZC, Fan J, Tang ZY, Zhou J, Qin LX, Wang JH, et al. A comparison of treatment combinations with and without radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombus. *Int J Radiat Oncol Biol Phys* 2005; **61**: 432–43. doi: <http://dx.doi.org/10.1016/j.ijrobp.2004.05.025>
 31. Kim TH, Kim DY, Park JW, Kim YI, Kim SH, Park HS, et al. Three-dimensional conformal radiotherapy of unresectable hepatocellular carcinoma patients for whom transcatheter arterial chemoembolization was ineffective or unsuitable. *Am J Clin Oncol* 2006; **29**: 568–75. doi: <http://dx.doi.org/10.1097/01.coc.0000239147.60196.11>
 32. Huang YJ, Hsu HC, Wang CY, Wang CJ, Chen HC, Huang EY, et al. The treatment responses in cases of radiation therapy to portal vein thrombosis in advanced hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2009; **73**: 1155–63. doi: <http://dx.doi.org/10.1016/j.ijrobp.2008.06.1486>
 33. Sieghart W, Huckle F, Pinter M, Graziadei I, Vogel W, Müller C, et al. The ART of decision making: retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma. *Hepatology* 2013; **57**: 2261–73. doi: <http://dx.doi.org/10.1002/hep.26256>