Risk Prediction of Radiation-Induced Hepatic Toxicity Complications in Patients With Hepatocellular Carcinoma

Chin-Shiuh Shieh

National Kaohsiung University of Science and Technology

Chi-Ming Chou

National Kaohsiung University of Science and Technology

Tai-Lin Huang

Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine

Chin-Hsueh Lin

National Kaohsiung University of Science and Technology

Pei-Ju Chao

National Kaohsiung University of Science and Technology

Jia-Ming Wu

Chengde Medical University

Chao-Hong Liu

National Kaohsiung University of Science and Technology

Stephen W Leung

National Kaohsiung University of Science and Technology

Chin-Dar Tseng

National Kaohsiung University of Science and Technology

Hsuan-Chih Hsu

Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine

Tsair-Fwu Lee (✉ tflee@nkust.edu.tw)

National Kaohsiung University of Science and Technology

Research Article

Keywords: Hepatocellular carcinoma, LASSO, Logistic Regression, Radiation - induced hepatic toxicity

Posted Date: December 2nd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-110762/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Risk prediction of radiation-induced hepatic toxicity complications in patients with hepatocellular carcinoma

Chin-Shiuh Shieh¹, Chi-Ming Chou^{1,2}, Tai-Lin Huang³, Chin-Hsueh Lin¹, Pei-Ju Chao^{1,2,4}, Jia-Ming Wu⁵,
Chao-Hong Liu^{1,6}, Stephen W Leung^{1,6}, Chin-Dar Tseng^{1,2}, Hsuan-Chih Hsu^{3,*} and Tsair-Fwu Lee^{1,2,7,*}

- ¹ Department of Electronics Engineering, National Kaohsiung University of Science and Technology, Kaohsiung, Taiwan, R.O.C.; csshie@nku.edu.tw (C.-S. S.); ee1008512@gmail.com (C.-M.C.); cslin@nku.edu.tw (C.-H. Lin); pjchao99@gmail.com (P.-J. C.); y4509@yuanhosp.com.tw (C.-H. Liu.); lwan@ms36.hinet.net (S.-W. L.); 1102405111@gm.kuas.edu.tw (C.-D. T.); tflee@nku.edu.tw (T.-F. L.)
- ² Medical Physics and Informatics Laboratory of Electronics Engineering, National Kaohsiung University of Science and Technology, Kaohsiung, Taiwan, R.O.C.; ee1008512@gmail.com (C.-M.C.); pjchao99@gmail.com (P.-J. C.); 1102405111@gm.kuas.edu.tw (C.-D. T.); tflee@nku.edu.tw (T.-F. L.)
- ³ Department of Hematology and Oncology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, 83342, Taiwan, R.O.C.; victorhtl@yahoo.com.tw (T.-L. H.); hsuan5@adm.cgmh.org.tw (H.-C. H.)
- ⁴ Department of Radiation Oncology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan, R.O.C.; pjchao99@gmail.com (P.-J. C.)
- ⁵ Department of Biomedicine Engineering, Chengde Medical University, Chengde City, 067000, Hebei Province, China.; jiaming.wu@chmsec.com (J.-M. W.)
- ⁶ Department of Dermatology, Kaohsiung Yuan's General Hospital, Kaohsiung, 80249, Taiwan, R.O.C.; y4509@yuanhosp.com.tw (C.-H. Liu.); lwan@ms36.hinet.net (S.-W. L.)
- ⁷ PhD program in biomedical engineering, Kaohsiung Medical University, Kaohsiung, Taiwan, R.O.C.; tflee@nku.edu.tw (T.-F. L.)
- * Correspondences: tflee@nku.edu.tw; hsuan5@adm.cgmh.org.tw

Received: date; Accepted: date; Published: date

Featured Application: This study shows that the dose-volume factors are effective in the risk of radiation-induced hepatic toxicity complications in patients with hepatocellular carcinoma.

Abstract: We use dose-volume factors to predict the risk of radiation-induced hepatic toxicity (RIHT) complications in patients with hepatocellular carcinoma (HCC) for controlling the low tolerance of liver organs to radiation and reducing the incidence of radiation-induced hepatic toxicity complications. This study retrospectively collected 114 patients who underwent Intensity Modulation Radiation Therapy (IMRT) for hepatocellular carcinoma between 2014 and 2017. The total number of patients was 69 after excluding normal liver organs whose volume did not reach 700 cc and extreme data. A total of 138 experimental samples were generated using the bootstrap method. All patients were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) during treatment to determine the degree of increase in blood draws and to judge for radiation-induced hepatic toxicity complications. The patient received dose-volume parameters were uniformly adjusted using a bioequivalent dose conversion of 2 Gy/fraction. The study data were divided into normal and total liver received dose-volume. Least absolute shrinkage and selection operator (LASSO) was used to select predictors and logistic regression (LR) was used to establish the performance model. LASSO was used to select the patient dose-volume parameter predictor. The risk factors of normal liver received dose-volume were age and NLV_{30 Gy}. The risk factors of total liver received dose-volume were age and TLV_{35 Gy}. For patients with hepatocellular carcinoma receiving radiation therapy (RT), this study recommends that a normal liver receiving a dose volume of 30 Gy should be less than 54.75%, so that the probability of RIHT can be less than 50%. A total liver receiving a dose volume of 35 Gy should be less than 54.75% so that the probability

of RIHT can be less than 50%. It can control the low tolerance of liver organs to radiation and reduce the incidence of hepatotoxic complications induced by radiotherapy techniques.

Keywords: Hepatocellular carcinoma, LASSO, Logistic Regression, Radiation - induced hepatic toxicity

1. Introduction

Hepatocellular carcinoma (HCC) was previously identified as a common cause of cancer-related death worldwide and accounts for more than 90% of the total number of major primary liver malignancies. The most common region for most of these HCC cases is Asia[1]. Therefore, HCC represents one of the leading cancer death issues in Asia.[2]

Radiation therapy (RT) of some liver organs in patients with HCC is unavoidable, but high energy radiation may cause damage to normal liver organs and cause the complication of radiation-induced hepatic toxicity (RIHT)[3]. Although it is not clear which dose-volume parameters can effectively reduce the induced liver organ damage, the main causes of radiation complications are due to RT[4]. Although most RIHT cases can be controlled through treatment, this complication can lead to worsened liver function and severe damage and lead to liver failure and death[5-7].

Therefore, the dose-volume parameters for HCC patients must be carefully evaluated before receiving RT treatment and setting a treatment plan. It is important to not only maximize the effective dose to the tumor but also to minimize the dose delivered to the surrounding normal liver. Predicting complication risks will be a considerable clinical advantage[6-8].

This study focused on the dose-volume factor risks of RIHT for HCC patients undergoing Intensity Modulation Radiation Therapy (IMRT). IMRT has improved the disadvantages of Three-Dimensional Conformal Radiation Therapy (3D-CRT) and can provide different size treatments and multiple high-precision beams released during the treatment[9,10]. It is currently a widely used technology in treating HCC[11].

A single dose factor was used to predict the probability of complications for patients with RIHT[12,13]. The single variable was used to analyze the liver volume receiving parameter to determine whether it was a significant risk factor for RIHT. Multivariate analysis was used to predict the dose-volume parameter that should be controlled after RT to reduce the chance of RIHT[14].

After obtaining the predictive risk factor model, we predicted the probability of complications caused by damage to normal tissue or the organ with normal tissue complication probability (NTCP) model[9,15]. Lyman Kutcher-Burma (LKB) was used for the NTCP model, including dose-volume distribution, dose-grading effect, and equivalent uniform dose (EUD) for coefficient evaluation[16-19]. This model effectively derives curve fitting to analyze increasing slope parameters (m) of prediction models, 50% complication rate of normal tissues received dose (TD_{50}), and 25% complication rate of normal tissues received dose (TD_{25}).

2. Materials and Methods

2.1. Patient characteristics

This study retrospectively collected 114 patients who underwent IMRT for HCC between 2014 and 2017. The total number of patients was 69 after excluding normal liver organs whose volume did not reach 700 cc and extreme data. A total of 138 experimental samples were generated using the bootstrap method. The diagnosis and evaluation of patients' complications were determined by the same physician based on their professional judgment. Patients with RIHT induced by RT were defined as significant factors[20,21]. Patients' characteristics are shown in Table 1 and treatment parameters of dose volume factors are shown in Table 2.

All experimental protocols of this study were approved by the institutional review board (IRB) of Chang Gung memorial hospital (201701811B0). Least absolute shrinkage and selection operator (LASSO) was used to select risk predictors. Furthermore, all risk predictors were established by two

algorithms, logistic regression (LR) and NTCP models. The area under the receiver operating characteristic curve (AUC), accuracy (ACC) and negative predictive value (NPV) were used to compare the system performance. The flow diagram of this study is shown in Figure 1.

Table 1. Patients' characteristics

Characteristics Factors		RIHT 0 (n = 50) Value (%)	RIHT 1 (n = 19) Value (%)	p - value
Age (y)	Mean	67.64	63.21	0.13
	Range	41-87	41-87	
	<51	2 (4)	2 (11)	
	51-60	10 (20)	6 (32)	
	61-70	18 (36)	7 (37)	
Gender	>70	20 (40)	4 (20)	0.46
	Male	38 (76)	16 (84)	
	Female	12 (24)	3 (16)	

Abbreviation: RIHT 1: Conforms to the Radiation - Induced Hepatic Toxicity, RIHT 0 : Incompatible to the Radiation - Induced Hepatic Toxicity

Table 2. Treatment parameters of dose volume factors

Dose Volume Factors	Mean	Range	Mean	Range	p - value
NL _{v5} Gy (%)	82.21	33-100	82.84	45-100	0.86
NL _{v10} Gy (%)	70.78	27 - 94	71.52	34 - 95	0.87
NL _{v15} Gy (%)	60.18	15 - 91	60.89	30 - 86	0.87
NL _{v20} Gy (%)	49.24	11 - 79	51.52	26 - 70	0.53
NL _{v25} Gy (%)	39.82	9 - 64	42.73	22 - 57	0.30
NL _{v30} Gy (%)	32.42	8 - 49	35.31	21 - 44	0.20
NL _{v35} Gy (%)	26.96	7 - 39	29.21	19 - 40	0.23
NL _{v40} Gy (%)	22.64	6 - 31	24.57	15 - 37	0.24
NL _{v45} Gy (%)	18.86	5 - 27	20.10	10 - 32	0.41
NL _{v50} Gy (%)	15.08	2 - 24	16.10	4 - 28	0.48
TL _{v5} Gy (%)	85.82	34 - 100	87.26	55 - 100	0.70
TL _{v10} Gy (%)	77.78	28 - 100	79.57	47 - 97	0.68
TL _{v15} Gy (%)	70.22	17 - 100	73.00	43 - 92	0.54
TL _{v20} Gy (%)	63.22	13 - 100	67.42	40 - 80	0.35
TL _{v25} Gy (%)	57.02	11 - 100	62.00	37 - 84	0.25
TL _{v30} Gy (%)	52.22	9 - 100	57.36	36 - 80	0.22
TL _{v35} Gy (%)	48.50	9 - 100	53.36	35 - 77	0.25
TL _{v40} Gy (%)	45.60	8 - 100	50.36	34 - 73	0.26
TL _{v45} Gy (%)	42.90	7 - 99	47.42	32 - 67	0.29
TL _{v50} Gy (%)	40.24	5 -96	44.05	30 - 59	0.24

Abbreviation: NL_{V5-50} Gy = normal liver volume receiving 5 – 50 Gy, TL_{V5-50} Gy = total liver volume receiving 5 – 50 Gy, step size 5 Gy.

2.2. Evaluation of RIHT complications

The incidences of all diseases were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for RIHT classification[22]. If the value before treatment was less than the normal standard value, the normal standard value was used as the reference value[23]. The normal standard reference values for blood tests are shown in Table 3[6].

The evaluation of liver function used the patient's blood test value as the standard basis. The blood draw timing was divided into pre-treatment, during the course of treatment, and after treatment (a total of eight times). Blood tests include glutamic oxaloacetic transaminase (GOT), glutamic acid pyruvic transaminase (GPT), and alkaline phosphatase (ALP) serum concentrations[24]. Among the three items, any grade ≥ 2 was eligible for RIHT 1, and all grades < 2 were RIHT 0.

Table 3. Normal standard reference values for blood test

Grade	GOT	GPT	ALP
0	≤ 37	≤ 40	40 - 140
1	$> 37 - 92.5$	$> 40 - 100$	$> 140 - 350$
2	$> 92.5 - 185$	$> 100 - 200$	$> 350 - 700$
3	$> 185 - 740$	$> 200 - 800$	$> 700 - 2800$

4	> 740	> 800	> 2800
5	death	death	death

Abbreviation: RIHT 1: Conforms to the Radiation - Induced Hepatic Toxicity, RIHT 0 : Incompatible to the Radiation - Induced Hepatic Toxicity

2.3. Radiation therapy

Patients underwent IMRT to treat HCC with a single radiation dose ranging from 1.8–3.5 Gy and an average total radiation dose of 70.2 Gy (ranging from 50–70.2 Gy). However, according to the patient's treatment plan, the biologically effective dose (BED) was used to convert each dose into a standard fractionated dose (2 Gy/time), and the ratio of dose conversion factor (α/β) for the liver was 3, as shown in (1)[25,26].

$$nd_1 \left(1 + \frac{d_1}{\alpha / \beta}\right) = nd_2 \left(1 + \frac{d_2}{\alpha / \beta}\right) \quad (1)$$

where n is the number of radiation treatments, d1 is the single-dose, d2 is the standard fractional dose, and α/β is the dose conversion factor.

2.4. Candidate factors

- Age
Patient age when receiving RT
- Gender
Patient gender
- Liver dose-volume receiving

During a patient receiving RT, the total liver volume receiving (TLV) minus the planning target volume (PTV) in the liver organ is the normal liver volume receiving ($NL_{V5-50 \text{ Gy}}$). In this analysis, the normal liver volume receiving prescribed dose was 5 - 50 Gy to the $NL_{V5-50 \text{ Gy}}$.

2.5. Statistical analysis

Continuous variable factors, such as patient age, gender, NLV, and TLV, were assessed using the independent sample t-Test[27] to identify significant differences in mean values and dependent variables.

LASSO was used to extract the factors of RIHT, as shown in (2). A LR prediction model was built using multiple variables, as shown in (3)[28-30].

$$\arg \min_{\beta} \sum_{t=1}^T \|Y - X\beta\|^2 \text{ subject to } \sum_{j=1}^k |\beta_j|^\alpha \leq t \quad (2)$$

$$\ln \left(\frac{P(Y = 1)}{1 - P(Y = 1)} \right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_p x_p \quad (3)$$

The individual models were evaluated using three evaluation methods to analyze the best model for inducing RIHT. The three evaluation methods were: ACC, as shown in (4); AUC, as shown in (5); and NPV, as shown in (6).

$$A = (TP + TN) / (TP + FP + FN + TN) \quad (4)$$

$$AUC = \frac{\sum_{ins \in \text{positiveclass}} \text{rank}_{ins_i} - \frac{M \times (M+1)}{2}}{M \times N} \quad (5)$$

$$NPV = \frac{specificity \times (1 - prevalence)}{(1 - sensitivity) \times prevalence + specificity \times (1 - prevalence)} \quad (6)$$

2.6. NTCP model

An EUD-based LKB NTCP models were used for the analyses[31], as shown in (7)[32]. The normal tissues and organs received a dose of 50% of the complication rate (TD_{50}) and model slope parameters (m) were obtained from the mode. μ is equal to the effective dose, defined as shown in (8).[33]

$$NTCP = c(u) = \frac{1}{\sqrt{2\pi}} \cdot \int_{-\infty}^u e^{-t^2/2} dt \quad (7)$$

$$u = \frac{EUD - TD_{50}}{m \cdot TD_{50}} \quad (8)$$

The original definition of the EUD was derived on the basis of a mechanistic formulation using a linear-quadratic cell survival model[34-36], with a phenomenological model of the form as follows,

$$EUD = \left(\sum_{i=1} (v_i D_i^a) \right)^{1/a} \quad (9)$$

Where v_i is unitless and stands for the i 'th partial volume receiving dose D_i in Gy; a is a unitless model parameter that is specific to the tumor or normal structure of interest. The relevant details described in the previous studies[37,38].

2.7. LR model

LR is a qualitative dependent variable regression model and suitable for handling binomial distribution problems. The model estimates the probability of suffering from RIHT and presents the outcome as a probability whose value is limited between 0 and 1 with a threshold value of 0.5. If the probability is greater than 0.5 then the patient has the complication of RIHT, otherwise they do not. The model is described in (10):

$$\ln \left(\frac{P_i}{1 - P_i} \right) = \beta_0 + \beta_1 \chi_1 + \dots + \beta_i \chi_i \quad (10)$$

where P_i means the probability of RIHT, χ_i means the predictive parameters and β_i means the parametric coefficients[39].

3. Results

3.1. Sample mean dose chart

The dose-volume histograms (DVH) of normal and total liver radiation receiving were established for the samples[40]. The mean dose conforming to RIHT 1 is higher than RIHT 0 regardless of normal and total liver received dose-volume, as shown in Figure 2.

3.2. Lasso factor selection

LASSO was used to extract predicted risk factors[41]. The non-zero factor coefficients in normal liver factors indicate that the impact is significant in the order age, $NLV_{30 \text{ Gy}}$, and $NLV_{35 \text{ Gy}}$. The non-zero factor coefficients in total liver factors indicate that the impact is significant in the order age, $TLV_{35 \text{ Gy}}$, and $TLV_{40 \text{ Gy}}$. The LASSO factor selection ranking is shown in Figure 3. According to the selected predictors, they are substituted into LR to establish a probability verification model for selecting the best combination of factors that induce RIHT.

In Figure 3A, 3C, coefficients were actually pushed to zero with lasso penalty for feature selection of normal liver factors and total liver factors, respectively. In Figure 3A, all 12 variables are in the model when $\log(\lambda)=2.56$, only 3 variables are retained and when $\log(\lambda)=0.31$. Identically, in Figure 3C, only 3 variables are retained and when $\log(\lambda)=0.23$. Consequently, lasso can be used to identify and extract those features with the largest (and most consistent) signal when a data set has many features.

The optimal value of lambda was found using minimization form of the cross-validation error to verify the model performs under different lambda values of normal liver factors and total liver factors, respectively, shown in Figure 3B, 3D. The plots display the cross-validation error according to the log of lambda. The left dashed vertical line indicates that the log of the optimal value of lambda is close to -4, which is the one that minimizes the prediction error. This lambda value will give the most accurate model.

3.3. The best prediction model

The LR model for predicting the risks of normal liver and total liver factors is shown in Table 4. For predicting the risks of normal liver, the combined prediction model using age and NLV_{30 Gy} binomial factors has the best performance, with an ACC value of 0.72, AUC value of 0.64, and NPV value of 0.73.

Table 4. LR model with select risk factors.

Normal liver	ACC	AUC	NPV
Age	.72	.62	.72
Age +NLV _{30 Gy}	.72	.64	.73
Age +NLV _{30 Gy} +NLV _{35 Gy}	.72	.64	.72
Total liver			
Age	.72	.62	.72
Age +TLV _{35 Gy}	.72	.64	.74
Age +TLV _{35 Gy} +TLV _{40 Gy}	.72	.64	.74

Abbreviation: NLV_{5-50 Gy} = normal liver volume receiving 5 – 50 Gy, TLV_{5-50 Gy} = total liver volume receiving 5 – 50 Gy, ACC = accuracy, AUC = the area under the receiver operating characteristic curve, NPV = negative predictive value.

For predicting the risks of total liver, the combined prediction model using age and TLV_{35 Gy} binomial factors has the best performance with an ACC value of 0.72, AUC value of 0.64, NPV value of 0.74.

3.4. Model coefficient and odds ratio

After analyzing the LR coefficient and odds ratio of RIHT induced by RT, age and RIHT were negatively correlated. Younger sample populations are more sensitive to RIHT. NLV_{30 Gy} and TLV_{35 Gy} have positive β values, indicating a positive correlation with complications. Patients receiving RT should be treated using the above dose-volume risk factors to prevent induced RIHT. Multiple logistic regression analysis coefficients and odds ratio of normal and total liver models with predictive factors are shown in Table 5.

Table 5. Multiple logistic regression analysis coefficients and odds ratio of normal and total liver models with predictive factors.

Normal liver	β	p-value	odds ratio	95% CI
Age	-0.04	0.19	0.97	0.92 – 1.02
NLV _{30 Gy}	0.04	0.28	1.04	0.97 – 1.12

Constant	-0.13	0.99	0.99	
Total liver				
Age	-0.04	0.15	0.96	0.91 – 1.01
TL _{V35 Gy}	0.02	0.28	1.02	0.98 – 1.06
Constant	0.52	0.79	1.69	

Abbreviation: NL_{V5-50 Gy} = normal liver volume receiving 5 – 50 Gy, TL_{V5-50 Gy} = total liver volume receiving 5 – 50 Gy, β = regression coefficient, 95% CI = 95% confidence interval.

3.5. Normal tissue complication probability model

LKB of NTCP models were established using the best normal liver and total liver risk factors to analyze the correlation of risk factors with RIHT[42].

The univariate dose-response fitted curve of normal liver (using NL_{V30 Gy}) for the incidence of RIHT patients treated with IMRT is shown in Figure 4. The parameters for the univariate NTCP regression model were calculated using the percentage and the absolute of the normal liver volume that received more than 30 Gy. According to the model curve, the tolerance of NL_{V30 Gy} producing a 50% complication rate (TD₅₀) was determined to be 54.75% in volume in HCC patients treated with IMRT. The tolerances corresponding to a 25% incidence of complications (TD₂₅) was 31.20%.

The univariate dose-response fitted curve of total liver (using TL_{V35 Gy}) for the incidence of RIHT patients treated with IMRT is shown in Figure 5. The parameters for the univariate NTCP regression model were calculated using the percentage and the absolute value of the normal liver volume that received more than 35 Gy. According to the model curve, the tolerance of TL_{V30 Gy} producing a 50% complication rate

(TD₅₀) was determined to be 87.40% in volume in HCC patients treated with IMRT. The tolerance corresponding to a 25% incidence of complications (TD₂₅) was 47.40%.

All figures and tables should be cited in the main text as Figure 1, Table 1, etc.

4. Discussion

In this study, the data revealed that the combined prediction model using age and NL_{V30 Gy} binomial factors has the best performance for predicting the risks of normal liver with NPV reaching 0.73, and using age and TL_{V35 Gy} binomial factors has the best performance for predicting the risks of total liver with NPV reaching 0.74.

Previous studies have reported a wide range of incidences of RIHT. The definition of RIHT is not exactly the same. In the reference, patients with HCC cannot avoid liver sensitivity problems during RT. Dose limitation is the most important solution to prevent RIHT[43]. In addition to limiting RT doses, patients with liver cirrhosis (LC, Child-Pugh B/C) have relatively poor tolerance to radiation. Patients with LC may have impeded damage repair after RT. In order to exclude confounding factors, LC factors were not considered in this study[8].

Radiation therapy is not widely used due to the low tolerance of the entire liver in the treatment of HCC patients. Song et al. reported 5-10% of patients receiving 30-35 Gy of whole liver radiation will experience RIHT[43]. However, the liver may be partially irradiated at higher doses with the development of radiation technology. Within an acceptable range of RIHT, an effective radiation dose can be provided. Since RIHT is still the most important dose-limiting factor, some clinical dosimetric parameters have been reported for predict RIHT. In radiation therapy of liver cancer, the dose-response relationship has been studied. Increasing the radiation dose of intrahepatic cancer can improve tumor control and survive. However, due to the combined effects of radiation therapy and chemotherapy, the dose increase seems to be severely limited. Ultimately, a more precise understanding of liver toxicity in current treatment may increase the radiation dose to the optimal level.

Benson et al.[44] analyzed and improved the risk factors for liver damage caused by radiation-induced liver disease (RILD) complications[45]. Independent-sample T-tests were used to analyze and compare continuous variables between patients with and without RILD[46-48]. The Fisher exact test was used to compare categorical variables[49].

It is the major reason for limiting the increase in radiation dose and re-irradiation of tumors located vicinity of the liver. However; in recent years, modern radiation therapy programs have allowed moderate dose escalation of these tumors. Various dosimetric constraints can be used to accurately predict toxicity. The Mean dose of 30 Gy is generally considered to be safe, but patients with abnormal liver function have low radiation tolerance to the liver. These patients are more likely to develop to RILD. RILD can be divided into two types,, classical (patients without underlying liver disease) and non-classical (patients with underlying liver disease).

In univariate analysis, the results showed that gender, age, portal vein thrombosis (PVT) and transarterial chemoembolization (TACE) were not statistically significant in correlations related to RILD (both $p > .05$).

However, the Fisher exact test demonstrated a statistically significant correlation between tumor stage and RILD ($p = .031$). Normal liver volume (NLV) and gross tumor volume (GTV) were also correlation with RILD ($p = .018$ and $.038$, respectively).

Lee et al.[50] compared the clinical results and toxicity of two different dose regimens after stereotactic body radiation therapy (SBRT) in the treatment of small HCC tumors (≤ 3 cm). In the study, 44 patients with local HCC who underwent SBRT were reviewed, including those unsuitable for surgery, whose liver volume was greater than 700 mL, and whose HCC confined to the liver without metastasis and LC (Child-Pugh A/B). The independent sample T-test, Chi-square test (χ^2 Test), Fisher Exact Test, or Mann-Whitney test were used for statistical analysis. Intrahepatic failure-free survival (IHFFS),

distant metastasis-free survival (DMFS), and overall survival (OS) were obtained using the Kaplan-Meier survival estimation method[20,51]. The 44 patients included 10 patients at 45 Gy and 34 patients at 60 Gy. The 1- and 3-year overall survival rates (OS) were 97.7% and 80.7%, failure-free survival rates (IHFFS) were 76% and 40.5%, and distant-free survival rates (DMFS) were 87.3% and 79.5%. However, local control is a favorable factor for tumor size ≤ 2 cm, $p = 0.041$. Benson et al. studied only dose-volume and did not have the same parameters as other clinical factors defined in the above reference[52]. However, Lee et al. pointed out that tumor size ≤ 2 cm at 45 Gy is quite different from this study. Patients had advanced cancer tumors. A mean tumor size > 6 cm may cause differences in dose-volume parameters that require more attention[44].

Radiation-induced hepatotoxicity is one of the most severe dose-limiting toxicities of HCC patients receiving RT. Although most RIHT cases are usually self-limiting and can be treated with supportive therapy, this complication may lead to a decline in liver reserve, moreover, in severe cases, may lead to liver failure and death. The prognosis of patients with liver cancer is related to the extent of tumor and liver remaining reserves. Therefore, when patients with HCC treated with RT, it is important not only to maintain a low dose to the liver, but also to deliver an effective radiation dose to the tumor. For avoiding RIHT, it is required both a better understanding of the biological properties of RIHT and the parameters that predict the occurrence of RIHT.

5. Conclusions

For patients with HCC receiving RT, to control the liver organs' low tolerance to radiation and reduce the incidence of RIHT, we recommend that a normal liver receiving a dose volume of 30 Gy should be less than 54.75% in volume so that the probability of RIHT can be less than 50%. The overall liver is recommended to receive a dose volume of 35 Gy and should be less than 87.40% in volume, which can make the probability of RIHT less than 50%.

Author Contributions: CMC, TLH, CHLin, PJC, CHLiu, SWL, CDT and JMW: technical supports on data collection and analysis; had provided valuable suggestions and revised the manuscript. HCH and PJC: supported the characterization of the samples, had provided valuable suggestions and revised the manuscript. CSS, HCH and TFL: supervised the project; had given valuable advices on the proceeding of this work; designed the concept and the experiment method of the research, wrote and revised the manuscript. All authors read and approved the final manuscript.

Funding: This research was funded by Ministry of Science and Technology (MOST) of the Executive Yuan of the Republic of China, in part, grants number MOST107-2221-E-992-014-MY2, MOST109-2221-E-992-011-MY2.

Acknowledgments: We thank Wei-Han Lu and Zih-Xiang Su for technical supports.

Conflicts of Interest: The authors declare no conflict of interest.

Data availability: The data supporting the results of this article are included within this manuscript and supplementary.

Ethical Statement: Institutional Review Board (IRB) approval was obtained from the Chang Gung memorial hospital IRB (approval number: 201701811B0), and the requirement for informed consent was waived given the retrospective nature of the study. All methods were carried out in accordance with relevant guidelines and regulations.

References

1. Yuen, M.F.; Hou, J.L.; Chutaputti, A. Hepatocellular carcinoma in the Asia pacific region. *Journal of gastroenterology and hepatology* 2009, 24, 346-353.
2. Omata, M.; Cheng, A.-L.; Kokudo, N.; Kudo, M.; Lee, J.M.; Jia, J.; Tateishi, R.; Han, K.-H.; Chawla, Y.K.; Shiina, S. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatology international* 2017, 11, 317-370.
3. Liang, S.-X.; Zhu, X.-D.; Xu, Z.-Y.; Zhu, J.; Zhao, J.-D.; Lu, H.-J.; Yang, Y.-L.; Chen, L.; Wang, A.-Y.; Fu, X.-L. Radiation-induced liver disease in three-dimensional conformal radiation therapy for primary liver carcinoma: the risk factors and hepatic radiation tolerance. *International Journal of Radiation Oncology* Biology* Physics* 2006, 65, 426-434.
4. Kanemoto, A.; Mizumoto, M.; Okumura, T.; Takahashi, H.; Hashimoto, T.; Oshiro, Y.; Fukumitsu, N.; Moritake, T.; Tsuboi, K.; Sakae, T. Dose-volume histogram analysis for risk factors of radiation-induced rib fracture after hypofractionated proton beam therapy for hepatocellular carcinoma. *Acta Oncologica* 2013, 52, 538-544.
5. Kim, J.Y.; Lim, Y.K.; Kim, T.H.; Cho, K.H.; Choi, S.H.; Jeong, H.; Kim, D.W.; Park, J.H.; Shin, D.H.; Lee, S.B. Normal liver sparing by proton beam therapy for hepatocellular carcinoma: Comparison with helical intensity modulated radiotherapy and volumetric modulated arc therapy. *Acta Oncologica* 2015, 54, 1827-1832.
6. Kim, T.H.; Kim, D.Y.; Park, J.-W.; Kim, S.H.; Choi, J.-I.; Kim, H.B.; Lee, W.J.; Park, S.J.; Hong, E.K.; Kim, C.-M. Dose-volumetric parameters predicting radiation-induced hepatic toxicity in unresectable hepatocellular carcinoma patients treated with three-dimensional conformal radiotherapy. *International Journal of Radiation Oncology* Biology* Physics* 2007, 67, 225-231.
7. Lee, J.-S.; Im, I.-C.; Kang, S.-M.; Goo, E.-H.; Baek, S.-M. Changes in the planning target volume and liver volume dose based on the selected respiratory phase in respiratory-gated radiation therapy for a hepatocellular carcinoma. *Journal of the Korean Physical Society* 2013, 63, 1832-1837.
8. Jung, J.; Yoon, S.M.; Kim, S.Y.; Cho, B.; Park, J.-h.; Kim, S.S.; Song, S.Y.; Lee, S.-w.; Do Ahn, S.; Choi, E.K. Radiation-induced liver disease after stereotactic body radiotherapy for small hepatocellular carcinoma: clinical and dose-volumetric parameters. *Radiation oncology* 2013, 8, 249.
9. Cheng, J.C.-H.; Wu, J.-K.; Huang, C.-M.; Liu, H.-S.; Huang, D.Y.; Tsai, S.Y.; Cheng, S.H.; Jian, J.J.-M.; Huang, A.T. Dosimetric analysis and comparison of three-dimensional conformal radiotherapy and intensity-modulated radiation therapy for patients with hepatocellular carcinoma and radiation-induced liver disease. *International Journal of Radiation Oncology* Biology* Physics* 2003, 56, 229-234.
10. Munden, R.F.; Erasmus, J.J.; Smythe, W.R.; Madewell, J.E.; Forster, K.M.; Stevens, C.W. Radiation injury to the liver after intensity-modulated radiation therapy in patients with mesothelioma: an unusual CT appearance. *American Journal of Roentgenology* 2005, 184, 1091-1095.
11. Rim, C.H.; Seong, J. Application of radiotherapy for hepatocellular carcinoma in current clinical practice guidelines. *Radiation oncology journal* 2016, 34, 160.
12. Kang, M.K.; Kim, M.S.; Kim, S.K.; Ye, G.W.; Lee, H.J.; Kim, T.N.; Eun, J.R. High-dose radiotherapy with intensity-modulated radiation therapy for advanced hepatocellular carcinoma. *Tumori Journal* 2011, 97, 724-731.
13. Park, J.M.; Kim, K.; Chie, E.K.; Choi, C.; Ye, S.-J.; Ha, S. RapidArc® vs intensity-modulated radiation therapy for hepatocellular carcinoma: a comparative planning study. *The British journal of radiology* 2012, 85, e323-e329.

14. Kim, J.W.; Han, K.-H.; Seong, J. Phase I/II trial of helical IMRT-based stereotactic body radiotherapy for hepatocellular carcinoma. *Digestive and Liver Disease* 2019, 51, 445-451.
15. Kuo, Y.-C.; Chiu, Y.-M.; Shih, W.-P.; Yu, H.-W.; Chen, C.-W.; Wong, P.-F.; Lin, W.-C.; Hwang, J.-J. Volumetric intensity-modulated Arc (RapidArc) therapy for primary hepatocellular carcinoma: comparison with intensity-modulated radiotherapy and 3-D conformal radiotherapy. *Radiation Oncology* 2011, 6, 76.
16. Eccles, C.L.; Bissonnette, J.-P.; Craig, T.; Taremi, M.; Wu, X.; Dawson, L.A. Treatment planning study to determine potential benefit of intensity-modulated radiotherapy versus conformal radiotherapy for unresectable hepatic malignancies. *International Journal of Radiation Oncology* Biology* Physics* 2008, 72, 582-588.
17. Kobashi, K.; Prayongrat, A.; Kimoto, T.; Toramatsu, C.; Dekura, Y.; Katoh, N.; Shimizu, S.; Ito, Y.M.; Shirato, H. Assessing the uncertainty in a normal tissue complication probability difference (Δ NTCP): radiation-induced liver disease (RILD) in liver tumour patients treated with proton vs X-ray therapy. *Journal of radiation research* 2018, 59, i50-i57.
18. Milano, M.T.; Chmura, S.J.; Garofalo, M.C.; Rash, C.; Roeske, J.C.; Connell, P.P.; Kwon, O.-H.; Jani, A.B.; Heimann, R. Intensity-modulated radiotherapy in treatment of pancreatic and bile duct malignancies: toxicity and clinical outcome. *International Journal of Radiation Oncology* Biology* Physics* 2004, 59, 445-453.
19. Wang, X.; Krishnan, S.; Zhang, X.; Dong, L.; Briere, T.; Crane, C.H.; Martel, M.; Gillin, M.; Mohan, R.; Beddar, S. Proton radiotherapy for liver tumors: dosimetric advantages over photon plans. *Medical Dosimetry* 2008, 33, 259-267.
20. Zhang, T.; Zhao, Y.-T.; Wang, Z.; Li, C.-R.; Jin, J.; Jia, A.Y.; Wang, S.-L.; Song, Y.-W.; Liu, Y.-P.; Ren, H. Efficacy and safety of intensity-modulated radiotherapy following transarterial chemoembolization in patients with unresectable hepatocellular carcinoma. *Medicine* 2016, 95.
21. Poorvu, P.D.; Sadow, C.A.; Townamchai, K.; Damato, A.L.; Viswanathan, A.N. Duodenal and other gastrointestinal toxicity in cervical and endometrial cancer treated with extended-field intensity modulated radiation therapy to paraaortic lymph nodes. *International Journal of Radiation Oncology* Biology* Physics* 2013, 85, 1262-1268.
22. Kim, J.W.; Seong, J.; Lee, I.J.; Woo, J.Y.; Han, K.-H. Phase I dose-escalation study of helical intensity-modulated radiotherapy-based stereotactic body radiotherapy for hepatocellular carcinoma. *Oncotarget* 2016, 7, 40756.
23. Chera, B.S.; Amdur, R.J.; Tepper, J.E.; Tan, X.; Weiss, J.; Grilley-Olson, J.E.; Hayes, D.N.; Zanation, A.; Hackman, T.G.; Patel, S. Mature results of a prospective study of deintensified chemoradiotherapy for low-risk human papillomavirus-associated oropharyngeal squamous cell carcinoma. *Cancer* 2018, 124, 2347-2354.
24. Faria, S.; Ruo, R.; Cury, F.; Duclos, M.; Souhami, L. Acute and late toxicity in high-risk prostate cancer patients treated with androgen suppression and hypofractionated pelvic radiation therapy. *Practical radiation oncology* 2017, 7, 264-269.
25. Lee, M.T.; Purdie, T.G.; Eccles, C.L.; Sharpe, M.B.; Dawson, L.A. Comparison of simple and complex liver intensity modulated radiotherapy. *Radiation oncology* 2010, 5, 115.
26. Kong, M.; Hong, S.E.; Choi, W.S.; Choi, J.; Kim, Y. Treatment outcomes of helical intensity-modulated radiotherapy for unresectable hepatocellular carcinoma. *Gut and liver* 2013, 7, 343.
27. Doi, H.; Masai, N.; Uemoto, K.; Suzuki, O.; Shiomi, H.; Tatsumi, D.; Oh, R.-J. Validation of the liver mean dose in terms of the biological effective dose for the prevention of radiation-induced liver damage. *Reports of Practical Oncology & Radiotherapy* 2017, 22, 303-309.
28. Menard, S. *Applied logistic regression analysis*; Sage: 2002; Vol. 106.
29. Zou, H. The adaptive lasso and its oracle properties. *Journal of the American statistical association* 2006, 101, 1418-1429.
30. Wang, H.; Feng, M.; Frey, K.A.; Ten Haken, R.K.; Lawrence, T.S.; Cao, Y. Predictive models for regional hepatic function based on ^{99m}Tc-IDA SPECT and local radiation dose for physiologic adaptive radiation therapy. *International Journal of Radiation Oncology* Biology* Physics* 2013, 86, 1000-1006.
31. Palma, G.; Monti, S.; Conson, M.; Pacelli, R.; Cella, L. Normal tissue complication probability (NTCP) models for modern radiation therapy. *Semin. Oncol.*
32. Daly, M.E.; Luxton, G.; Choi, C.Y.; Gibbs, I.C.; Chang, S.D.; Adler, J.R.; Soltys, S.G. Normal tissue complication probability estimation by the Lyman-Kutcher-Burman method does not accurately predict

- spinal cord tolerance to stereotactic radiosurgery. *International Journal of Radiation Oncology* Biology* Physics* 2012, 82, 2025-2032.
33. Dijkema, T.; Raaijmakers, C.P.; Ten Haken, R.K.; Roesink, J.M.; Braam, P.M.; Houweling, A.C.; Moerland, M.A.; Eisbruch, A.; Terhaard, C.H. Parotid gland function after radiotherapy: the combined Michigan and Utrecht experience. *International Journal of Radiation Oncology* Biology* Physics* 2010, 78, 449-453.
34. Lee, T.-F.; Chao, P.-J.; Wang, C.-Y.; Lan, J.-H.; Huang, Y.-J.; Hsu, H.-C.; Sung, C.-C.; Su, T.-J.; Lian, S.-L.; Fang, F.-M. Dosimetric comparison of helical tomotherapy and dynamic conformal arc therapy in stereotactic radiosurgery for vestibular schwannomas. *Medical Dosimetry* 2011, 36, 62-70.
35. Wu, Q.; Mohan, R.; Niemierko, A.; Schmidt-Ullrich, R. Optimization of intensity-modulated radiotherapy plans based on the equivalent uniform dose. *International Journal of Radiation Oncology* Biology* Physics* 2002, 52, 224-235.
36. Gay, H.A.; Niemierko, A. A free program for calculating EUD-based NTCP and TCP in external beam radiotherapy. *Physica Medica* 2007, 23, 115-125.
37. Lee, T.-F.; Chao, P.-J.; Wang, H.-Y.; Hsu, H.-C.; Chang, P.; Chen, W.-C. Normal tissue complication probability model parameter estimation for xerostomia in head and neck cancer patients based on scintigraphy and quality of life assessments. *BMC cancer* 2012, 12, 567.
38. Lee, T.-F.; Fang, F.-M. Quantitative analysis of normal tissue effects in the clinic (QUANTEC) guideline validation using quality of life questionnaire datasets for parotid gland constraints to avoid causing xerostomia during head-and-neck radiotherapy. *Radiotherapy and Oncology* 2013, 106, 352-358.
39. Gaja, H.; Liou, F. Defect classification of laser metal deposition using logistic regression and artificial neural networks for pattern recognition. *The International Journal of Advanced Manufacturing Technology* 2018, 94, 315-326.
40. Chen, D.; Wang, R.; Meng, X.; Liu, T.; Yan, H.; Feng, R.; Liu, S.; Jiang, S.; Xu, X.; Zhu, K. A comparison of liver protection among 3-D conformal radiotherapy, intensity-modulated radiotherapy and RapidArc for hepatocellular carcinoma. *Radiation Oncology* 2014, 9, 48.
41. Tseng, H.-H.; Luo, Y.; Ten Haken, R.K.; El Naqa, I. The role of machine learning in knowledge-based response-adapted radiotherapy. *Frontiers in Oncology* 2018, 8, 266.
42. Petersen, J.B.; Lassen, Y.; Hansen, A.T.; Muren, L.P.; Grau, C.; Høyer, M. Normal liver tissue sparing by intensity-modulated proton stereotactic body radiotherapy for solitary liver tumours. *Acta Oncologica* 2011, 50, 823-828.
43. Lawrence, T.S.; Robertson, J.M.; Anscher, M.S.; Jirtle, R.L.; Ensminger, W.D.; Fajardo, L.F. Hepatic toxicity resulting from cancer treatment. *International Journal of Radiation Oncology* Biology* Physics* 1995, 31, 1237-1248.
44. Benson, R.; Madan, R.; Kilambi, R.; Chander, S. Radiation induced liver disease: a clinical update. *Journal of the Egyptian National Cancer Institute* 2016, 28, 7-11.
45. Lo, S.S.; Dawson, L.A.; Kim, E.Y.; Mayr, N.A.; Wang, J.Z.; Huang, Z.; Cardenes, H.R. Stereotactic body radiation therapy for hepatocellular carcinoma. *Discovery medicine* 2010, 9, 404-410.
46. Peiffert, D.; Baumann, A.-S.; Marchesi, V. Treatment of hepatic metastases of colorectal cancer by robotic stereotactic radiation (Cyberknife®). *Journal of visceral surgery* 2014, 151, S45-S49.
47. Murphy, J.D.; Hattangadi-Gluth, J.; Song, W.Y.; Vollans, E.; Camborde, M.-L.; Kosztyla, R.; Loewen, S.K.; Crumley, C.; Moiseenko, V. Liver toxicity prediction with stereotactic body radiation therapy: The impact of accounting for fraction size. *Practical radiation oncology* 2014, 4, 372-377.
48. Byun, H.K.; Kim, H.J.; Im, Y.R.; Han, K.-H.; Seong, J. Dose escalation by intensity modulated radiotherapy in liver-directed concurrent chemoradiotherapy for locally advanced BCLC stage C hepatocellular carcinoma. *Radiotherapy and Oncology* 2019, 133, 1-8.
49. Kim, J.Y.; Chung, S.M.; Choi, B.O.; Kay, C.S. Hepatocellular carcinoma with portal vein tumor thrombosis: improved treatment outcomes with external beam radiation therapy. *Hepatology Research* 2011, 41, 813-824.
50. Lee, K.H.; Yu, J.I.; Park, H.C.; Park, S.Y.; Shin, J.S.; Shin, E.H.; Cho, S.; Jung, S.H.; Han, Y.Y.; Lim, D.H. Is higher dose always the right answer in stereotactic body radiation therapy for small hepatocellular carcinoma? *Radiation oncology journal* 2018, 36, 129.
51. Dawood, O.; Mahadevan, A.; Goodman, K.A. Stereotactic body radiation therapy for liver metastases. *European Journal of Cancer* 2009, 45, 2947-2959.
52. Shirai, S.; Sato, M.; Noda, Y.; Kumayama, Y.; Shimizu, N. Incorporating GSA-SPECT into CT-based dose-volume histograms for advanced hepatocellular carcinoma radiotherapy. *World journal of radiology* 2014, 6, 598.

Figures

Figure 1

Flow diagram. Abbreviation: RIHT = radiation - induced hepatic toxicity, LKB = Lyman Kutcher-Burma, HCC = hepatocellular carcinoma, GOT = glutamic oxaloacetic transaminase, GPT = glutamic pyruvic transaminase, ALP = alkaline phosphatase, TD50 = 50% of the complication rate, TD25 = 25% incidence of complications.

Figure 2

Normal and total liver relative volume of receiving DVH. Abbreviation: RIHT 1 = conforms to the radiation - induced hepatic toxicity, RIHT 0 = incompatible to the radiation - induced hepatic toxicity, DVH = dose-volume histograms.

Figure 3

(A) (C) The coefficients shrinkage for feature selection of normal liver factors and total liver factors, respectively. (B) (D) Cross validation to verify the model performs under different lambda values of normal liver factors and total liver factors, respectively. Abbreviation: RIHT 1 = conforms to the radiation - induced hepatic toxicity, RIHT 0 = incompatible to the radiation - induced hepatic toxicity, LKB = Lyman Kutcher-Burma, NTCP = normal tissue complication probability, TD50 = 50% of the complication rate, TD25 = 25% incidence of complications.

Figure 4

The fitted dose-response curves of LKB NTCP models for NLV30 Gy. Abbreviation: RIHT 1 = conforms to the radiation - induced hepatic toxicity, RIHT 0 = incompatible to the radiation - induced hepatic toxicity, LKB = Lyman Kutcher-Burma, NTCP = normal tissue complication probability, TD₅₀ = 50% of the complication rate, TD₂₅ = 25% incidence of complications.

Figure 5

The fitted dose-response curves of LKB NTCP models for TLV35 Gy. Abbreviation: RIHT 1 = conforms to the radiation - induced hepatic toxicity, RIHT 0 = incompatible to the radiation - induced hepatic toxicity, LKB = Lyman Kutcher-Burma, NTCP = normal tissue complication probability, TD₅₀ = 50% of the complication rate, TD₂₅ = 25% incidence of complications.