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Original Article

The normal tissue complication probability model-based approach considering uncertainties for the selective use of radiation modality in primary liver cancer patients

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ABSTRACT

Purpose: To predict the probability of radiation-induced liver toxicity (RILT) and implement the normal tissue complication probability (NTCP) model-based approach considering confidence intervals (CIs) to select patients for new treatment techniques, such as proton beam therapy, based on a certain NTCP reduction (ΔNTCP) threshold for primary liver cancer patients.

Methods and materials: Common Toxicity Criteria for Adverse Events (CTCAE) grade ≥2 RILT was scored. The Lyman NTCP models predicting the probability of CTCAE grade ≥2 RILT as a function of the fraction-size adjusted mean liver dose (MLD), using reference fraction size = 2 Gy/fraction and α/β ratio = 2 Gy, were fitted using the maximum likelihood method. At certain combinations of MLDs, ΔNTCP with a CI was evaluated by the delta method.

Results: Of the 239 patients, the incidence of CTCAE grade ≥2 RILT was 55% (46% in the Child–Pugh (CP)-A vs. 81% in the CP-B/C, $p < 0.001$). Among 180 CP-A patients, 40% who had viral hepatitis infections experienced toxicity vs. 32% in the nonhepatitis subgroup. The MLD was 18 Gy in the toxicity group vs. 16.1 Gy in the nontoxicity group ($p = 0.002$). The estimated NTCP model parameters specific to the patient subgroups and the ΔNTCP with CI assuming a particular CP classification and viral hepatitis infection status were considerably different which possible changed treatment decision.

Conclusions: Patients with CP-A and viral hepatitis infection or CP-B/C cirrhosis had greater susceptibility to CTCAE grade ≥2 RILT. The estimated NTCP and ΔNTCP for individual patients along with a consideration of uncertainties improve the reliability of the NTCP model-based approach.

Charged particle therapy (CPT), proton beam therapy (PBT) and carbon ion therapy have been recognized as the most effective radiotherapy (RT) options for primary liver cancers, with demonstrated excellent tumor control and limited severe adverse outcomes because of the physical and biological advantages of these modalities [1,2]. However, due to the high treatment cost and lim-

Abbreviations: CPT, charged particle therapy; PBT, proton beam therapy; RT, radiotherapy; XRT, X-ray treatment; MBA, model-based approach; NTCP, normal tissue complication probability; ΔNTCP, NTCP reduction; RILT, radiation-induced liver toxicity; HCC, hepatocellular carcinoma; CCA, cholangiocarcinoma; 3D, three-dimensional; CP, Child–Pugh; HBV, hepatitis B virus; HCV, hepatitis C virus; 3D-CRT, 3D-conformal radiotherapy; IMRT, intensity-modulated radiotherapy; CT, computed tomography; ITV, internal target volume; DEBH, deep expiratory breath hold; IRB, institutional review board; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; UNL, upper normal limit; CTCAE, Common Toxicity Criteria for Adverse Events; RILD, radiation-induced liver disease; DVHs, Dose–volume histograms; FED, fraction-size equivalent dose; MLD, mean liver dose; V_x, volume receiving x Gy; OS, Overall survival; HL, Hosmer–Lemeshow; CI, confidence interval; $\Delta NTCP_{68\%CI}$ LB, 68%CI lower boundary of the ΔNTCP.

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ited facilities for CPT, appropriate patient selection is mandatory. Considering the lack of randomized control trials comparing CPT with standard X-ray treatment (XRT) in patients with liver cancers, an alternative model-based approach (MBA) is currently appealing in the radiation oncology field for allocating the suitable treatment modality for individual patients [3–5]. To identify patients who will likely benefit from new treatment modality such as PBT, a normal tissue complication probability (NTCP)-based MBA can be performed. Briefly, the dose distributions from the PBT and XRT plan are applied to the developed NTCP model of the toxicity outcome of interest and compared. The decreased dose to normal tissue from PBT is then transformed into a reduced complication risk, referred to as NTCP reduction (ΔNTCP). The treatment selection will be performed based on the predefined threshold of ΔNTCP. This approach has been recently studied for the selective use of PBT in head and neck cancer patients [6–8].

For liver cancer, the well-known NTCP model for radiation-induced liver toxicity (RILT) is the Lyman model [9]. At this moment, the model from Michigan University [10] is de facto standard, however, model parameters vary among studies [10–14]. The inherent impact of intrinsic biological factors such as liver cirrhosis and viral hepatitis infection on the radiosensitivity of liver tissue has been reported [15,16], suggesting a different dose–response relationship in individual patients. Additionally, several factors are associated with uncertainty of the model, which affects the accuracy of PBT selection [17]. Underestimating these values can eliminate any benefit gained from PBT, whereas an overly cautious practice might lead to unnecessary treatment. Therefore, the current study aimed to estimate the NTCP values and ΔNTCP with uncertainties in individualized subgroups to improve the reliability of the model prediction in the general population and to improve the clinical implementation of patient selection for PBT.

Materials and methods

Patients and treatment

Patient eligibility criteria included (i) diagnosis of primary liver cancers (hepatocellular carcinoma, HCC, and cholangiocarcinoma, CCA); (ii) Eastern Cooperative Oncology Group 0–2; (iii) completion of an RT course; (iv) available three-dimensional (3D) dosimetric parameters; and (v) available follow-up data for tumor and liver toxicity, with at least 4 months of follow-up for nontoxicity patients. Patients with progressive disease during a 4-month follow-up were excluded from the study. Demographic data, including age, gender, Child–Pugh (CP) score, viral hepatitis B and C (HBV and HCV) infection status, baseline liver function and follow-up data were collected. A serum virology diagnosis of HBV chronic infection was defined as positivity for HBV surface antigen (>0.2 ng/mL by chemiluminescent microparticle immunoassay, Abbott Diagnostics, Lake Forest, IL, USA), and HCV infection was defined as a positive anti-HCV status.

All patients received conformal external beam therapy techniques including 3D-conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), volumetric arc therapy, and stereotactic body radiotherapy. A planning computed tomography (CT) scan was acquired with patient immobilization. Target volumes were contoured using contrast-enhanced CT scans with a margin expanded to account for subclinical disease, set up uncertainty and respiratory motion. An additional internal target volume (ITV) was considered for the traditional free-breathing technique until the deep expiratory breath hold (DEBH) technique along with Vision RT (Varian, Palo Alto, CA, USA) was used to track the patients' surfaces during radiation (since January 2015). RT was delivered with a 10-MV or 15-MV linear accelerator. Treatment verification was performed at first fraction then weekly using cone-beam CT.

This study was approved by the institutional review board of Faculty of Medicine, Chulalongkorn University (IRB no. 602/60).

RILT

After the completion of RT, a routine follow-up was performed every 1–3 months for treatment-related toxicity or progression of disease. The endpoint of this study was grade ≥2 RILT defined as an elevation of liver transaminases (aspartate aminotransferase, AST, and alanine aminotransferase, ALT) more than 3 times the upper normal limit (3×UNL), an elevation of alkaline phosphatase (ALP) more than 2.5×UNL, or an elevation of total bilirubin more than 1.5×UNL according to Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03 in the absence of documented progressive disease. The severity or grading of RILT was scored for each test, and the maximum grade represented the toxicity grading of the individual patient. For another commonly used criterion, radiation-induced liver disease (RILD) was classified into classic RILD and nonclassic RILD [18]. Clinical manifestation of classic RILD included anicteric hepatomegaly, ascites, and elevated ALP more than 2×UNL. Non-classic RILD, usually described in patients with pretreatment poor liver function (CP-B/C), involved AST or ALT more than 5×UNL within 3 months after therapy, or liver function deterioration measured by a decline in CP score by 2 or more.

Lyman NTCP model for the prediction of RILT

Dose–volume histograms (DVHs) of the normal liver tissue (total liver volume minus gross tumor volume) of all patients were obtained from the Eclipse planning system version 8.6 (Varian Medical Systems, Palo Alto, CA, USA). To correct for the difference in treatment regimen, the physical dose distributions were converted to fraction-size equivalent dose (FED) using the linear quadratic model (α/β ratio of 2.0 Gy) at a reference fraction size of 2 Gy/fraction [19]. The mean liver dose (MLD) was a cumulative result of FED in each dose bin associated with partial volume associated in that particular dose bin (supplement 1). Due to a large volume effect (n close to 1.0) of liver tissue, we fixed the parameter n in the Lyman NTCP model at 1.0, known as MLD-based NTCP [10,13,14,20].

The dose–response relationship between MLD and CTCAE grade ≥2 RILT was modeled by a sigmoid-shaped Lyman NTCP model, as follows [9,21]:

$$\mathrm{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-x^2/2} dx \tag{1}$$

with

$$t = \frac{(MLD - TD_{50})}{m \cdot TD_{50}} \tag{2}$$

where $TD_{50}$is the 50% tolerance dose and the parameter m is the steepness of the dose–response curve at TD_{50}.

NTCP reduction (ΔNTCP) function

With the MLD derived from the treatment plan and the estimated Lyman NTCP parameters(TD_{50} and m) from the maximal likelihood estimation, the ΔNTCP of PBT compared with XRT is given by the following function:

$$f(\mathrm{XRT}, \mathrm{PBT}) = \mathrm{NTCP}_{\mathrm{XRT}}\ (\mathrm{MLD}_{\mathrm{XRT}} | TD_{50}, m) - \mathrm{NTCP}_{\mathrm{PBT}}\ (\mathrm{MLD}_{\mathrm{PBT}} | TD_{50}, m)$$

where f is a function of ΔNTCP. MLD_{XRT} and MLD_{PBT} denote the mean dose to the normal liver for a certain patient for XRT and PBT plans, respectively.

Statistical analysis

Clinical characteristics and dosimetric parameters between patients with or without toxicity were compared using a χ^2 test or t-test. The correlation between RILT (CTCAE grade) and RILD was tested by Spearman's rank correlation. Univariate and multivariate analysis was performed using the logistic regression model (multivariate selection: enter method with a probability of entry of 0.20). Due to the multicollinearity between dosimetric parameters, MLD and volume receiving x Gy (V_x), only one variable was included in the logistic regression model at each time. A p-value of <0.05 was considered statistically significant. Overall survival (OS) was estimated from the date of treatment to the date of death or last follow-up using the Kaplan–Meier method.

Normal liver DVH and the occurrence or lack of occurrence of RILT composed the input data for determining the Lyman NTCP model parameters TD_{50} and m using maximum likelihood estimation [22] for the entire dataset as well as specific subgroups. Subsequently, the variance (σ^2) and covariance of parameters were obtained from the observed Fisher information matrix. The Hosmer–Lemeshow (HL) goodness-of-fit test was used to evaluate the fitted NTCP model [23]. Model performance was demonstrated using area under the receiver operating characteristic curve (AUC). The ΔNTCP between two radiation modalities considering the confidence interval (CI) was described in our previous study and in supplement 2 [24]. Briefly, given the ΔNTCP of certain combinations of MLDs and the estimated variance and covariance matrix, the delta method was applied for estimating the CI of ΔNTCP [25]. Statistical analyses were conducted in R version 3.4.2 (Team, 2010) [26] and IBM SPSS statistics (version 22.0, SPSS, Inc., Chicago, IL).

Table 1
Patient and treatment characteristics (N = 239).

Characteristics	Value (%)
Age	
Mean ± SD (years)	60.3 ± 12.5
Gender	
Male	175 (73.2%)
Female	64 (26.8%)
Child–Pugh classification	
A	180 (75.3%)
B-C	59 (24.7%)
Viral hepatitis infection	95 (39.7%)
Diagnosis	
Hepatocellular carcinoma	146 (61.1%)
Cholangiocarcinoma	93 (38.9%)
Radiotherapy technique	
3D-CRT	117 (49%)
IMRT/VMAT/SBRT	122 (51%)
Fraction size	
≤3 Gy	180 (75.3%)
>3 Gy	59 (24.7%)
Radiation treatment	
Total prescription dose (Gy), median (IQR)	45 (30–50)
Number of fractions (fractions), median (IQR)	10 (10–25)
Dose per fraction (Gy), median (IQR)	3 (1.8–3.5)
Normal liver volume* (cc), median (IQR)	1100.7 (890.7–1418.1)

3D-CRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; VMAT = volumetric arc radiotherapy; SBRT = stereotactic body radiotherapy; SD = standard deviation; IQR = interquartile range
* Normal liver volume = total liver volume minus gross liver volume.

Results

Between June 2007 and February 2017, 239 patients (146 with HCC and 93 with CCA) were eligible for this study. The majority of the patients were male (73.2%) and CP-A (75.3%). HBV/HCV infection was found in 95 patients (39.7%). The median prescription dose was 45 Gy in a daily fraction of 1.8–10 Gy. There were 5 patients treated with whole liver RT at 8 Gy in a single fraction. Demographic data are shown in Table 1.

RILT

At the median follow-up time of 10.8 months, a total of 131/239 patients (54.8%) developed CTCAE grade ≥2 RILT or liver dysfunction equivalent to CTCAE grade ≥2 RILT after RT, namely, 83/180 (46.1%) in the CP-A group and 48/59 (81.4%) in the CP-B/C group (p < 0.001). Among 95 patients with viral hepatitis infection, 60 patients (63.2%) experienced CTCAE grade ≥2 RILT, which was significantly higher than the 49.3% of patients without infection (p = 0.035). Forty-seven patients were diagnosed with RILD (19.7%): 16/180 patients (8.9%) in the CP-A group vs. 31/59 patients (52.5%) in the CP-B/C group (p < 0.001). There was a correlation between CTCAE-RILT and RILD by the Spearman rank test (r = 0.393, p < 0.001). Patients who developed a CTCAE grade ≥2 RILT outcome had shorter median OS, specifically, 8 months vs. 17.5 months (p < 0.001).

In the multivariate analysis, CP classification, normal liver volume, MLD, V_5, V_{10} and V_{20} were significantly associated with CTCAE grade ≥2 RILT. CP classification was the strongest predictor with an odds ratio of 5.55 (p < 0.001). Table 2 summarizes the association between clinical and DVH parameters and CTCAE grade ≥2 RILT.

NTCP and ΔNTCP

For the MLD-based Lyman model, the estimated TD_{50} and m parameters were inconsistent among patient subgroups. The estimated parameters are summarized in Table 3. CP-A patients were divided into two subgroups: CP-A, the nonhepatitis subgroup (N = 116), and CP-A, the hepatitis subgroup (N = 64). The analysis was not performed in the CP-B/C subgroup after stratification by hepatitis status due to the limited number of patients. All models in every subgroup fit the clinical data well (χ^2_{HL} = 6.90, p = 0.547 for the CP-A, nonhepatitis subgroup; χ^2_{HL}=7.50, p = 0.483 for the CP-A, hepatitis subgroup; and χ^2_{HL} 10.54, p = 0.229 for the CP-B/C subgroup). Overall model performance was acceptable with AUC of 0.714 (95%CI, 0.650–0.779) compared with AUC of 0.569 (95% CI, 0.496–0.642) when using Michigan's parameters [10]. Large differences in the NTCP curves were seen among subgroups stratified by CP classification and viral hepatitis infection status (Fig. 1).

At a certain combination of MLDs, the mean values of NTCP were adopted to obtain the ΔNTCP. Then, the uncertainty of ΔNTCP was acquired by the delta method, which considered the variance and covariance matrix of the NTCP parameters. To give an example of implementing our ΔNTCP contours in clinical practice, we applied the DVH data of HCC tumors from a dosimetric study comparing PBT vs. IMRT plans performed by Toramatsu et al. [27]. The calculated ΔNTCP with a 68% CI predicting CTCAE grade ≥2 RILT between two radiation modalities is listed for 5 patients in Table 4. In Fig. 2, every spot on the contour line represents the ΔNTCP = 10%, the so-called iso-ΔNTCP contour, and the area to the right and below this contour is considered a PBT-benefit area. Assuming a different CP classification and status of viral hepatitis infection, the iso-ΔNTCP contours were totally different.

Table 2
Univariate and multivariate analysis for clinical and dosimetric variables associated with grade ≥2 radiation-induced liver toxicity.

Characteristics	Radiation-induced liver toxicity		p-value	
	Grade <2 (*N* = 108)	Grade ≥2 (*N* = 131)	UVA	MVA
Age (years)	60.8 ± 12.8	59.9 ± 12.3	0.541	–
Gender			0.542	–
Male	77	98		
Female	31	33		
Diagnosis			0.017	0.913
Hepatocellular carcinoma	56	88		
Intrahepatic cholangiocarcinoma	52	43		
Child–Pugh and viral hepatitis subgroups			<0.001	<0.001
Child–Pugh A, non-hepatitis	58	44		
Child–Pugh A, hepatitis	37	34		
Child–Pugh B and C	13	53		
Portal vein thrombosis (*N* = 110)	34	76	<0.001	0.034
Previous surgery (*N* = 69)	43	26	0.001	0.557
Transarterial chemoembolization (TACE) (*N* = 87)	42	45	0.277	–
Chemotherapy (*N* = 40)	18	22	1.000	–
RT technique			0.973	–
3D-CRT	53	64		
IMRT/VMAT/SBRT	55	67		
Gross tumor volume (cc)	220.6	553.1	0.001	0.171
Normal liver volume* (cc)	1107.6 ± 333.1	1302.7 ± 721.9	0.006	0.209
Mean MLD to liver (Gy)	16.1 ± 7.3	18.0 ± 7.3	0.041	0.017
V_{5Gy} (%)	59.4 ± 23.6	67.8 ± 22.5	0.005	0.006
V_{10Gy} (%)	47.7 ± 22.9	55.8 ± 24.1	0.009	0.025
V_{20Gy} (%)	31.0 ± 18.1	34.9 ± 19.1	0.105	0.149
V_{30Gy} (%)	20.5 ± 14.0	21.9 ± 15.6	0.478	–
V_{40Gy} (%)	12.1 ± 10.5	11.5 ± 11.2	0.675	–
V_{50Gy} (%)	4.6 ± 6.6	4.1 ± 7.0	0.572	–
$V_{50\%}$	46.1 ± 21.8	56.1 ± 24.3	0.001	0.016

UVA = univariate analysis; MVA = multivariate analysis; RT = radiotherapy; 3D-CRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; VMAT = volumetric arc therapy; SBRT = stereotactic body radiotherapy; MLD = mean liver dose; $V_{x\ Gy}$ = volume receiving x Gy; $V_{50\%}$ = volume receiving 50% of prescription dose.
* Normal liver volume = total liver volume minus gross liver volume.

Table 3
Lyman NTCP model parameters for predicting grade ≥2 radiation-induced liver toxicity of the whole group and subgroups.

	Parameters	
	TD_{50} (Gy)	*m*
Whole group (*N* = 239)	11.8	3.70
Child–Pugh A, nonhepatitis (*N* = 116)	28.0	1.97
Child–Pugh A, hepatitis (*N* = 64)	16.2	0.68
Child–Pugh B* (*N* = 59)	0.2	99.89

NTCP = normal tissue complication probability; TD_{50} = 50% tolerance dose for irradiation to the whole liver; *m* = steepness of the dose–response curve at TD_{50}.
* A TD_{50} slightly closer to zero and a larger value of m can be obtained as another converged maximum likelihood estimation solution, but the shape of the curve and its CI were almost equivalent to this set of parameters.

Discussion

Radiation-induced hepatitis is a dose-limiting complication of traditional liver-directed RT and can lead to deterioration of liver function followed by liver failure and death [10,18,28,29]. Therefore, predicting the risk of RILT in individual patients with unique clinical characteristics would facilitate treatment decision-making regarding the RT modality/technique/regimen. Intrinsic biological factors, such as poor hepatic functional reserve and chronic viral hepatitis, were reported to have a potential effect on the susceptibility of liver tissue to irradiation after 3D-CRT [15,16,30–32]. Our study showed the differential influence of biosusceptibility factors to RILT, consistent with these studies. We demonstrated the use of the Lyman NTCP model to estimate the risk of CTCAE grade ≥2 RILT as a function of the MLD and reported the new sets of estimated NTCP parameters for CTCAE grade ≥2 RILT for specific patient subgroups, i.e., the CP-A, nonhepatitis subgroup; the CP-A, hepatitis subgroup; and the CP-B/C subgroup.

To select patients who will gain a clinical benefit from PBT, Langendijk et al. has proposed a stepwise approach, referred to as the MBA [3]. This principle has been given attention by the health authorities of the Netherlands [4,5] with a threshold for clinical benefit considered as a predicted reduction in the probability of grade ≥2 toxicity of >10% (a total reduction of ≥15% for the complication profile) [8].

In this study, we contoured the ΔNTCP with a 68% CI at 10% ΔNTCP of developing CTCAE grade ≥2 RILT in liver cancer patients as an example of implementing this approach. As shown in Table 4 and Fig. 2, assuming a different CP classification and viral hepatitis infection status, the NTCP and ΔNTCP markedly varied and thus may have a potential impact on the decision regarding PBT use. For example, for plan ID 2 in Table 4 (MLD = 33.1 Gy for the IMRT plan vs. 20.1 Gy for the PBT plan), considering a ΔNTCP threshold of 10% reduction in CTCAE grade ≥2 RILT, PBT was indicated for patients with CP-A, hepatitis (ΔNTCP = 30.2%) and CP-B/C (ΔNTCP = 10.1%) but not for the CP-A, nonhepatitis subgroup (ΔNTCP = 9.4%). This finding emphasizes the differential benefit from PBT according to patient subgroup and the importance of appropriate patient selection. Of note, Toramatsu et al. applied Michigan NTCP parameters for RILD and corrected fraction size to 1.5 Gy/fraction with an α/β ratio of 2.5 Gy.

Moreover, there are considerable sources of model uncertainties and statistical assumptions from a small subset of patients

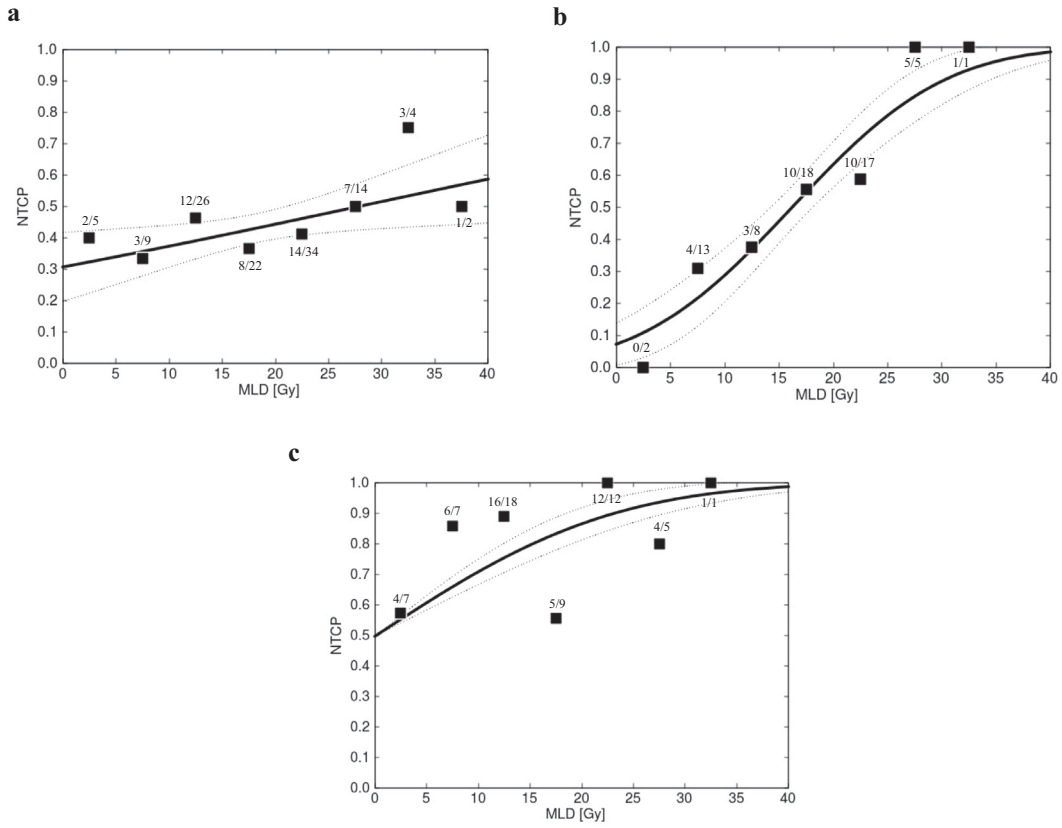

Fig. 1. The incidence of CTCAE grade ≥2 RILT or liver dysfunction equivalent to CTCAE grade ≥2 RILT of Child–Pugh A patients without (a) and with (b) viral hepatitis infection subgroups and Child–Pugh B/C patients (c) subgroups as a function of the MLD. The solid line represents the probability of CTCAE grade ≥2 RILT according to the NTCP model. The dotted lines represent the 68% CI of the fitted NTCP curve. CTCAE = common toxicity criteria of adverse events; RILT = radiation-induced liver toxicity; MLD = mean liver dose; NTCP = normal tissue complication probability; CI = confidence interval.

Table 4
The normal tissue complication probability reduction (ΔNTCP) with a 68% confidence interval for predicting the probability of CTCAE grade ≥2 RILT from two different treatment modalities assuming a different CP classification and viral hepatitis infection status.

Plan ID	Mean MLD IMRT (Gy)	Mean MLD SSPT (Gy)	ΔNTCP (68% CI) for CTCAE grade ≥2 RILT		
			Child–Pugh A, nonhepatitis	Child–Pugh A, hepatitis	Child–Pugh B/C
1	35.9	20.2	11.5% (1.6%–21.5%)	33% (28%–38%)	11.2% (8.3%–14.1%)
2	33.1	20.1	9.4% (1.2%–17.5%)	30.2% (25.5%–34.9%)	10.1% (7.9%–12.4%)
3	30.3	16.6	10.1% (1.3%–18.8%)	39.1% (31.5%–46.8%)	13.6% (11.9%–15.4%)
4	32.8	15.2	12.9% (1.7%–24.1%)	47.9% (39.2%–56.6%)	17.1% (14.9%–19.3%)
5	37.9	19.9	13% (1.8%–24.1%)	34.2% (28.9%–39.5%)	11.7% (8.5%–15%)

ΔNTCP = NTCP reduction; CI = confidence interval; CTCAE = common toxicity criteria of adverse events; RILT = radiation-induced liver toxicity; MLD = mean liver dose; IMRT = intensity-modulated radiotherapy; SSPT = spot-scanning proton therapy.

when developing the model [10,17,33,34]. The true population-based dose–response relationship can be estimated by the upper and lower limits of the CI, which improves the reliability of the model prediction in the general population. In the example in Table 4, if the 68%CI lower boundary of the ΔNTCP ($\Delta NTCP_{68\%CI}$ LB) was compared with the 10% ΔNTCP threshold, PBT was indicated for all patients in the CP-A with hepatitis subgroup ($\Delta NTCP_{68\%CI}$ LB = 25.5%) but not in the CP-A with nonhepatitis subgroup and two CP-B/C patients ($\Delta NTCP_{68\%CI}$ LB = 1.2% and 7.9%, respectively). Our results showed that the model-based approach using ΔNTCP can be implemented in the clinic with more confidence about its uncertainty (supplement 3). However, the appropriate ΔNTCP threshold considering CI for the selective use of PBT is still unknown. Consequently, the desired goal and challenge are to determine the threshold for identifying patients who would most likely benefit from PBT. The physical dose distribution, biological impact of the treatment on tumor and normal tissues, clinical impact on patients' quality of life and socioeconomic aspects need to be considered and optimized [35]. As a future research, we should perform cost-effective analysis of our model-based approach to improve quality-adjusted life years of patients and also total cost of national medical care.

This study has several strengths. First, the use of the delta method, which considers the variance and covariance of NTCP

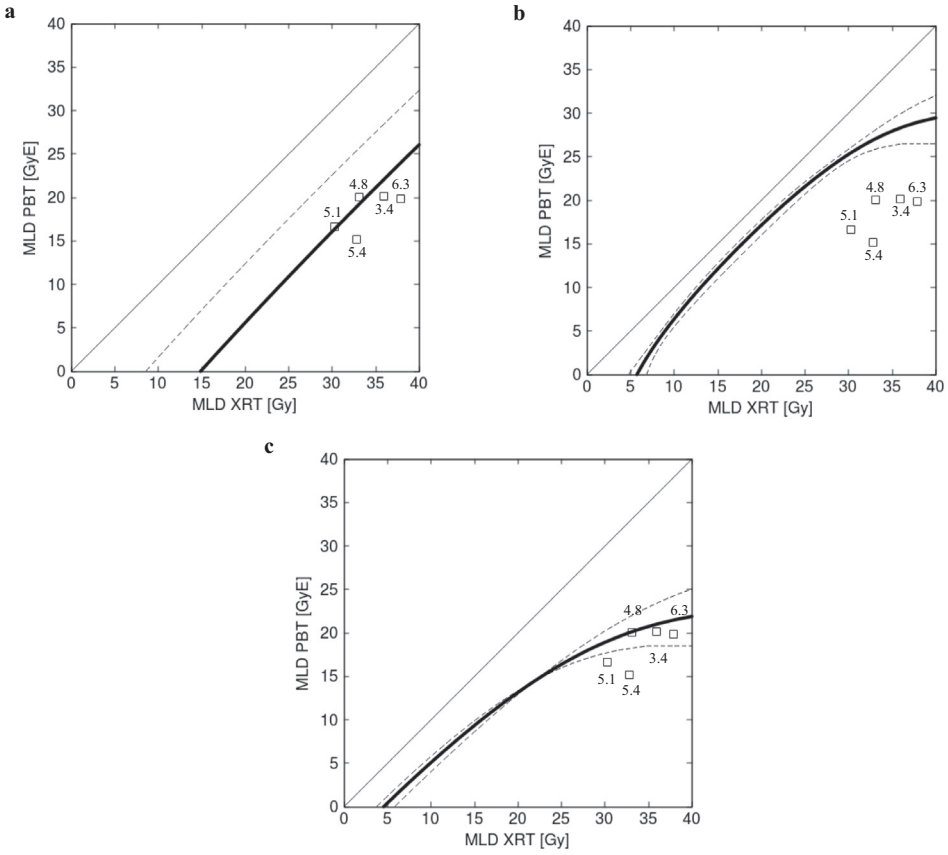

Fig. 2. The ΔNTCP of CTCAE grade ≥2 RILT between two radiation modalities of certain combinations of the MLD in Child–Pugh A patients without (a) and with (b) viral hepatitis infection subgroups and Child–Pugh B/C patients (c). The solid gray line is the MLD-equivalent line between XRT and PBT. The solid black line represents the iso-ΔNTCP contour at a 10% difference of CTCAE grade ≥2 RILT between XRT and PBT, where the area to the right of this contour line represents the area with a more than 10% difference. The dotted lines represent the 68% CI of the iso-ΔNTCP contour. The small box represents the size of tumors (cm) plotted according to their MLD from the XRT and PBT plans from the Toramatsu study. ΔNTCP = normal tissue complication probability reduction; CTCAE = common toxicity criteria of adverse events; RILT = radiation-induced liver toxicity; MLD = mean liver dose size; CI = confidence interval; XRT = X-ray therapy; PBT = proton beam therapy.

parameters, produced an NTCP curve estimation and ΔNTCP with a CI that are less overestimated and more easily generalizable than those of other methods. Second, unlike previously reported studies on NTCP for liver toxicity [10–15], our model predicts the probability of CTCAE grade ≥2 RILT as a function of the MLD. This outcome is based on a widely accepted standard toxicity criterion that is objective, easily assessable and convenient for data collection. Besides, CTCAE grade ≥2 RILT was moderately correlated with RILD but earlier detected, which might raise the concern of treating physician prior to develop severe changes of liver function. Third, the use of the MLD with the fraction-size normalization method mitigates the limitation of comparing DVH data between various fractionation regimens and eliminates the need for *n* optimization in the Lyman model. However, given the different physical and biological properties between PBT vs. XRT and the effect of changes in dose distributions on the predictive power of the NTCP model, the XRT-derived NTCP models should be validated prior to the direct comparison of toxicity risks [7]. Thus, multi-institutional data pooling is required, and the use of CTCAE and MLD helps facilitate data sharing among institutions.

The limitations of our study were the lack of data in the high (>45 Gy)-dose bin and the small patient number after stratification into subgroups. It was also noted that some patients had liver dysfunction equivalent to CTCAE grade ≥2 RILT despite a very low MLD. This high background, up to 50% in CP-B/C patients, might be due to pre-existing poor hepatic function, reactivation of viral hepatitis or rapid tumor reaction and might not be related to radiation. However, the background was eventually subtracted when calculating the ΔNTCP. In addition, despite stratification according to two clinical factors (CP classification and viral hepatitis infection status), our NTCP models considered only MLD to predict the RILT. Other possible prognostic or predictive parameters for RILT include tumor size and origin, portal vein thrombosis, and previous treatment [10,32] which justify the development of a multivariable model in our future work to accurately predict RILT in various circumstances. Another limitation was a lack of model validation in this analysis. It is important to validate our model using a validation dataset as a next step.

Among the clinical parameters, CP classification was the strongest predictive factor for risk of toxicity after liver RT, followed by viral hepatitis infection. We reported the estimated Lyman NTCP model parameters specific to patient subgroups stratified by CP classification and viral hepatitis infection status. NTCP curves with a 68%CI were determined for each subgroup, considering the variance and covariance of parameters. The ΔNTCP at a certain combination of MLDs (including its uncertainty) might be helpful to guide the selective use of PBT. Further study to establish the predefined, nationally agreed-upon selection criteria for PBT based on the expected ΔNTCP threshold are necessary.

Conflict of interest statement

S.S. and H.S. report grants from Hitachi, Ltd., all outside the submitted work. K.K. is an employee of the research institute of Hitachi, Ltd., in the field of radiological imaging but currently works for Hokkaido University Hospital under a secondment

agreement. K.K. declares that the submitted work has no relationship to Hitachi, Ltd. All other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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References

[1] Durante M, Orecchia R, Loeffler JS. Charged-particle therapy in cancer: clinical uses and future perspectives. Nat Rev Clin Oncol 2017;14:483–95.
[2] Igaki H, Mizumoto M, Okumura T, Hasegawa K, Kokudo N, Sakurai H. A systematic review of publications on charged particle therapy for hepatocellular carcinoma. Int J Clin Oncol 2018;23:423–33.
[3] Langendijk JA, Lambin P, De Ruysscher D, Widder J, Bos M, Verheij M. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. Radiother Oncol 2013;107:267–73.
[4] Widder J, van der Schaaf A, Lambin P, Marijnen CA, Pignol JP, Rasch CR, et al. The quest for evidence for proton therapy: model-based approach and precision medicine. Int J Radiat Oncol Biol Phys 2016;95:30–6.
[5] Grau C. The model-based approach to clinical studies in particle radiotherapy-a new concept in evidence based radiation oncology? Radiother Oncol 2013;107:265–6.
[6] Jakobi A, Bandurska-Luque A, Stutzer K, Haase R, Löck S, Wack LJ, et al. Identification of patient benefit from proton therapy for advanced head and neck cancer patients based on individual and subgroup normal tissue complication probability analysis. Int J Radiat Oncol Biol Phys 2015;92:1165–74.
[7] Blanchard P, Wong AJ, Gunn GB, Garden AS, Mohamed ASR, Rosenthal DI, et al. Toward a model-based patient selection strategy for proton therapy: External validation of photon-derived normal tissue complication probability models in a head and neck proton therapy cohort. Radiother Oncol 2016;121:381–6.
[8] Cheng Q, Roelofs E, Ramaekers BLT, Eekers D, van Soest J, Lustberg T, et al. Development and evaluation of an online three-level proton vs photon decision support prototype for head and neck cancer – comparison of dose, toxicity and cost-effectiveness. Radiother Oncol 2016;118:281–5.
[9] Lyman JT. Complication probability as assessed from dose-volume histograms. Radiat Res Suppl 1985;8:S13–9.
[10] Dawson LA, Normolle D, Balter JM, McGinn CJ, Lawrence TS, Ten Haken RK. Analysis of radiation-induced liver disease using the Lyman NTCP model. Int J Radiat Oncol Biol Phys 2002;53:810–21.
[11] Lawrence TS, Ten Haken RK, Kessler ML, Robertson JM, Lyman JT, Lavigne ML, et al. The use of 3-D dose volume analysis to predict radiation hepatitis. Int J Radiat Oncol Biol Phys 1992;23:781–8.
[12] Cheng JC, Liu HS, Wu JK, Chung HW, Jan GJ. Inclusion of biological factors in parallel-architecture normal-tissue complication probability model for radiation-induced liver disease. Int J Radiat Oncol Biol Phys 2005;62:1150–6.
[13] Xu ZY, Liang SX, Zhu J, Zhu XD, Zhao JD, Lu HJ, et al. Prediction of radiation-induced liver disease by Lyman normal-tissue complication probability model in three-dimensional conformal radiation therapy for primary liver carcinoma. Int J Radiat Oncol Biol Phys 2006;65:189–95.
[14] Tai A, Erickson B, Li XA. Extrapolation of normal tissue complication probability for different fractionations in liver irradiation. Int J Radiat Oncol Biol Phys 2009;74:283–9.
[15] Cheng JC, Wu JK, Lee PC, Liu HS, Jian JJ, Lin YM, et al. Biologic susceptibility of hepatocellular carcinoma patients treated with radiotherapy to radiation-induced liver disease. Int J Radiat Oncol Biol Phys 2004;60:1502–9.
[16] Dawson LA. Protons or photons for hepatocellular carcinoma? Let's move forward together. Int J Radiat Oncol Biol Phys 2009;74:661–3.
[17] Bijman RG, Breedveld S, Arts T, Astreinidou E, de Jong MA, Granton PV, et al. Impact of model and dose uncertainty on model-based selection of oropharyngeal cancer patients for proton therapy. Acta Oncol 2017;56:1444–50.
[18] Pan CC, Kavanagh BD, Dawson LA, Li XA, Das SK, Miften M, et al. Radiation-associated liver injury. Int J Radiat Oncol Biol Phys 2010;76:S94–S100.
[19] Tome WA, Fenwick JD. Analysis of radiation-induced liver disease using the Lyman NTCP model: in regard to Dawson et al. IJROBP 2002;53:810-821. Int J Radiat Oncol Biol Phys 2004;58:1318–9.
[20] Seppenwoolde Y, Lebesque JV, de Jaeger K, Belderbos JS, Boersma LJ, Schilstra C, et al. Comparing different NTCP models that predict the incidence of radiation pneumonitis. Normal tissue complication probability. Int J Radiat Oncol Biol Phys 2003;55:724–35.
[21] Kutcher GJ, Burman C, Brewster L, Goitein M, Mohan R. Histogram reduction method for calculating complication probabilities for three-dimensional treatment planning evaluations. Int J Radiat Oncol Biol Phys 1991;21:137–46.
[22] Carolan M, Oborn B, Foo K, Haworth A, Gulliford S, Ebert MA. An MLE method for finding LKB NTCP model parameters using Monte Carlo uncertainty estimates. J Phys: Conf Ser 2014;489:012087.
[23] Borst GR, Ishikawa M, Nijkamp J, Hauptmann M, Shirato H, Onimaru R, et al. Radiation pneumonitis in patients treated for malignant pulmonary lesions with hypofractionated radiation therapy. Radiother Oncol 2009;91:307–13.
[24] Kobashi K, Prayongrat A, Kimoto T, Toramatsu C, Dekura Y, Katoh N, et al. Assessing the uncertainty in a normal tissue complication probability difference (ΔNTCP): radiation[HYPHEN]induced liver disease (RILD) in liver tumour patients treated with proton vs X-ray therapy. J Radiat Res 2018;59:i50–7.
[25] Armitage P, Berry G, Matthews J. Statistical methods in medical research. 4th ed. United Kingdom: Wiley-Blackwell; 2001.
[26] Development Core R, Team R. A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2010.
[27] Toramatsu C, Katoh N, Shimizu S, Nihongi H, Matsuura T, Takao S, et al. What is the appropriate size criterion for proton radiotherapy for hepatocellular carcinoma? A dosimetric comparison of spot-scanning proton therapy versus intensity-modulated radiation therapy. Radiother Oncol 2013;8:48.
[28] Tanguturi SK, Wo JY, Zhu AX, Dawson LA, Hong TS. Radiation therapy for liver tumors: ready for inclusion in guidelines? Oncologist 2014;19:868–79.
[29] Cheng JC, Wu JK, Huang CM, Huang DY, Cheng SH, Lin YM, et al. Radiation-induced liver disease after radiotherapy for hepatocellular carcinoma: clinical manifestation and dosimetric description. Radiother Oncol 2002;63:41–5.
[30] Burman C, Kutcher GJ, Emami B, Goitein M. Fitting of normal tissue tolerance data to an analytic function. Int J Radiat Oncol Biol Phys 1991;21:123–35.
[31] Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991;21:109–22.
[32] Liang SX, Zhu XD, Xu ZY, Zhu J, Zhao JD, Lu HJ, et al. Radiation-induced liver disease in three-dimensional conformal radiation therapy for primary liver carcinoma: the risk factors and hepatic radiation tolerance. Int J Radiat Oncol Biol Phys 2006;65:426–34.
[33] Schilstra C, Meertens H. Calculation of the uncertainty in complication probability for various dose-response models, applied to the parotid gland. Int J Radiat Oncol Biol Phys 2001;50:147–58.
[34] Wedenberg M. Assessing the uncertainty in QUANTEC's dose-response relation of lung and spinal cord with a bootstrap analysis. Int J Radiat Oncol Biol Phys 2013;87:795–801.
[35] Shirato H, Le QT, Kobashi K, Prayongrat A, Takao S, Shimizu S, et al. Selection of external beam radiotherapy approaches for precise and accurate cancer treatment. J Radiat Res 2018;59:i2–i10.