Clinical and Translational Radiation Oncology 35 (2022) 70–75

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Original Research Article

A study on predicting cases that would benefit from proton beam therapy in primary liver tumors of less than or equal to 5 cm based on the estimated incidence of hepatic toxicity

Yusuke Uchinami [a], Norio Katoh [a,*], Ryusuke Suzuki [b], Takahiro Kanehira [b], Masaya Tamura [b], Seishin Takao [b], Taeko Matsuura [b], Naoki Miyamoto [b], Yoshihiro Fujita [c], Fuki Koizumi [c], Hiroshi Taguchi [c], Koichi Yasuda [c], Kentaro Nishioka [d], Isao Yokota [e], Keiji Kobashi [d], Hidefumi Aoyama [a]

[a] Department of Radiation Oncology, Hokkaido University Faculty of Medicine, North 15 West 7, Kita-ku, Sapporo, Hokkaido 060-8638, Japan
[b] Department of Medical Physics, Hokkaido University Hospital, North 14 West 5, Kita-ku, Sapporo, Hokkaido 060-8648, Japan
[c] Department of Radiation Oncology, Hokkaido University Hospital, North 14 West 5, Kita-ku, Sapporo, Hokkaido 060-8648, Japan
[d] Department of Radiation Medical Science and Engineering, Hokkaido University Faculty of Medicine, North 15 West 7, Kita-ku, Sapporo, Hokkaido 060-8638, Japan
[e] Department of Biostatistics, Hokkaido University Graduate School of Medicine, North 15 West 7, Kita-ku, Sapporo, Hokkaido 060-8638, Japan

ARTICLE INFO

Keywords:
Primary liver tumors
NTCP model
Model-based selection

ABSTRACT

Background: For small primary liver tumors, favorable outcomes have been reported with both of proton beam therapy (PBT) and X-ray therapy (XRT). However, no clear criteria have been proposed in the cases for which and when of PBT or XRT has to be used. The aim of this study is to investigate cases that would benefit from PBT based on the predicted rate of hepatic toxicity.

Materials and methods: Eligible patients were those who underwent PBT for primary liver tumors with a maximum diameter of $\leq$ 5 cm and Child-Pugh grade A (n = 40). To compare the PBT-plan, the treatment plan using volumetric modulated arc therapy was generated as the XRT-plan. The rate of predicted hepatic toxicity was estimated using five normal tissue complication probability (NTCP) models with three different endpoints. The differences in NTCP values (ΔNTCP) were calculated to determine the relative advantage of PBT. Factors predicting benefits of PBT were analyzed by logistic regression analysis.

Results: From the dose-volume histogram comparisons, an advantage of PBT was found in sparing of the normal liver receiving low doses. The factors predicting the benefit of PBT differed depending on the selected NTCP model. From the five models, the total tumor diameter (sum of the target tumors), location (hepatic hilum vs other), and number of tumors (1 vs 2) were significant factors.

Conclusions: From the radiation-related hepatic toxicity, factors were identified to predict benefits of PBT in primary liver tumors with Child-Pugh grade A, with the maximum tumor diameter of $\leq$ 5 cm.

Introduction

In primary liver tumors, photon-based stereotactic body radiotherapy has been widely used and reported to have favorable treatment results [1–5]. For a more precise treatment, proton beam therapy (PBT) has also been applied, and improved results have been reported [6–9]. Due to its physical properties, PBT can be expected to reduce the dose to the normal liver. However, no clear criteria have been proposed for selecting PBT or X-ray therapy (XRT). For the clinical validation of the added value of PBT to prevent adverse events, it is important to appropriately select cases that would benefit from the PBT [10].

In making the appropriate treatment decision, in selecting PBT or

Abbreviations: ALBI, albumin-bilirubin; CTV, clinical target volume; CP, Child-Pugh; DVH, dose-volume histogram; GTV, gross tumor volume; GyE, Gy equivalent; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiotherapy; NTCP, normal tissue complication probability; PBT, proton beam therapy; PTV, planning target volume; RBE, relative biological effectiveness; RILD, radiation-induced liver disease; VMAT, Volumetric modulated arc therapy; XRT, X-ray therapy.

* Corresponding author.
E-mail addresses: uchinamiy@med.hokudai.ac.jp (Y. Uchinami), noriwokatoh@med.hokudai.ac.jp (N. Katoh).

https://doi.org/10.1016/j.ctro.2022.05.004
Received 1 February 2022; Received in revised form 2 May 2022; Accepted 13 May 2022
Available online 17 May 2022

XRT, model-based selection has been proposed [11,12]. This strategy attempts to calculate the predicted rate of adverse events in PBT and XRT using normal tissue complication probability (NTCP) models. If the absolute difference in NTCP values (ΔNTCP) is greater than a predetermined criterion, PBT is considered advantageous and selected. In lung or brain tumors, several studies have compared the treatment plans of PBT and XRT, and these have shown the superiority of PBT in terms of NTCP [13,14]. In liver tumors, studies based on the risk of radiation-induced liver disease (RILD) was also reported, and these indicate that PBT may be superior in large tumors [15,16]. In these studies, however, the analysis was conducted using a single NTCP model, and the baseline liver function was not considered. Moreover, the benefits of PBT have not been established for small tumors (maximum diameter $\leq$ 5 cm). For the clinical application of model-based selection in liver tumors, we thought it necessary to conduct the study in a setting of actual clinical practice and propose criteria for cases that would benefit from PBT.

The aim of this study is to investigate benefits of cases with PBT from the perspective of radiation-related hepatic toxicity. We generated the XRT plans in simulations and discuss the merits of PBT using five NTCP models with different endpoints.

Materials and methods

Patients

This study was approved by the Ethics Review Committee of Hokkaido University Hospital (IRB number: 019–0455). The patients included in this study were with primary liver tumors of a maximum tumor diameter of 5 cm, treated with PBT at our institution from March 2015 to April 2021 (Table 1). Due to the small number of patients with Child-Pugh (CP) grade B, only cases with CP grade A were included in the analysis. The dose prescriptions were: 66 GyE in 10 fractions, 72.6 GyE in 22 fractions, or 76 GyE in 20 fractions. The fraction regimen of 20 or 22 was selected for patients with tumors in the hilar region or close to the gastrointestinal tract (GI-tract).

Proton beam therapy.

At our institution, we have used a combination of spot-scanning proton therapy and implanted fiducial markers in respiratory-moving tumors [17]. The treatment planning CT was non-contrast enhanced and scanned with the natural expiratory phase of the respiration cycle. Unless medically compromised, contrast-enhanced CT and/ or enhanced MRI was performed at the same respiratory phase and integrated into the treatment planning CT.

Table 1
Patient backgrounds.

Liver tumor	
Hepatocellular carcinomas	36 (90.0%)
Intrahepatic cholangiocarcinomas	4 (10.0%)
Baseline ALBI grade	
1	23 (57.5%)
2	17 (42.5%)
Treated lesions (At one time)	
One	31 (77.5%)
Two	9 (22.5 %)
Tumor location	
Hilum*	22 (55.0%)
Others	18 (45.0%)
Maximum tumor diameter (median, mm)	29.5 (range: 6–50)
Total tumor diameter (median, mm)	30.5 (range: 6–72)
Total GTV volume (median cm^3)	1.7 (range: 0.1 – 7.1)
Normal Liver volume (median, cm^3)	1268.8 (range 751.28–2473.4)
Dose prescription	
72.6 GyE in 22 fractions	16 (40.0%)
76.0 GyE in 20 fractions	13 (32.5%)
66.0 GyE in 10 fractions	11 (27.5%)

*Within 20 mm of main stem or first branch of the portal vein. ALBI: albumin-bilirubin, GTV: gross tumor volume, GyE: gray equivalent

In target contouring, the gross tumor volume (GTV) was defined as the tumor identified from each image, and the clinical target volume (CTV) was defined as the GTV with a 0–5 mm margin depending on the case. Specifically, we reduced the CTV margin in cases where liver function would be expected to deteriorate (e.g. large tumor volume, or small liver volumes after surgical resection). At this process, we removed the area of the CTV that does not overlap with the liver. In determining the dose prescription of XRT for the purpose of this study, the planning target volume (PTV) in XRT-plan was also generated in PBT-plan.

The dose prescription for the PBT-plan was basically given for 99% of the CTV volume (CTV D99). In some cases, dose prescriptions were based on D50 of the CTV due to its proximity to the the gastrointestinal tract. The relative biological effectiveness (RBE) of 1.1 was used. The dose constraint for a normal liver (Liver - GTV) was a mean dose of $<$ 30 Gy equivalent (GyE, 20–22 fractions) or $<$ 25 GyE (10 fractions). The details of the PBT-plan and dose constraints are shown in Table 2.

In the planning, the PBT-plans were optimized with single-field uniform dose optimization with two or three beams with a VQA version 3.077 (Hitachi Ltd., Tokyo). The intensity-modulated proton therapy (IMPT) by multifield optimization was also used for two cases where the tumor is close to the GI-tract. A margin of 5 mm including internal and setup margins was applied lateral to the beam direction. Distal and proximal margins, which were calculated as 3.5% of the range plus 1 mm, were added to account for range uncertainties.

X-ray simulation

Volumetric modulated arc therapy (VMAT) plans were generated as simulated X-ray plans (XRT-plan). The XRT-plan was generated using the Auto-Planning module of Pinnacle^3 in the treatment planning system Pinnacle^3 version 9.14 (Philips, Amsterdam, Netherlands). Several studies have already reported that the Auto-Planning module is comparable to manual planning for various sites [18,19] including the liver [20,21]. Since the NTCP value largely depends on the liver dose, we attempted to reduce the mean liver dose as far as possible without upsetting the overall balance (Supplementary material A). In the XRT-plan, the treatment planning CT and contouring were the same as those used in the PBT-plan. The planning target volume (PTV) was basically defined as the CTV with a 5-mm margin around the entire circumference.

To make a fair comparison, the dose prescriptions were set to be the same for XRT and PBT. In cases with doses prescribed for CTV D99 in the PBT-plan, the dose received by 95% of the PTV volume (PTV D95) was also recorded, and the same dose was prescribed to the of 95% of the PTV volume in XRT-plan. In the case of CTV D50 in the PBT-plan, the PTV D50 dose was prescribed for the XRT-plan. The details of the XRT-plan provided are in Supplementary materials A and B.

NTCP Model selection

In choosing the NTCP model for the radiation-related hepatic toxicity, we investigated multiple models with different endpoints. The Dawson model [22] is the most widely used. We also selected the Cheng and Xu models, which estimate the NTCP value based on the baseline CP

Table 2
General dose constraints in the PBT-plans.

Organ at risk	Constraints (RBE)		
		20–22 fractions	10 fractions
Normal liver (Liver – GTV)	Mean	$<$ 30GyE	$<$25GyE
Stomach	$D_{0.5cc}$	$<$ 60GyE	$<$47GyE
Duodenum	$D_{0.5cc}$	$<$ 50GyE	$<$40GyE
Intestine	$D_{0.5cc}$	$<$ 50GyE	$<$40GyE

GTV: gross tumor volume, PBT: proton beam therapy, RBE: relative biological effectiveness. Doses were normalized to 2-Gy (RBE) equivalent doses, using a linear quadric model with an α/β ratio of 3.

grade [23,24]. The endpoint of these models is ≥ grade 3 RILD, but it is desirable to use the NTCP model with different endpoints such as for the CP score and ALBI grade, which are more commonly used indicators in modern radiotherapy. There is the Pursley et al. proposed novel NTCP models where the endpoints increase in ≥ 2 CP scores or in the ≥ 1 albumin-bilirubin (ALBI) grades [25], and we used two of these NTCP models as they more closely reflect hepatic toxicities in the modern radiotherapy era. Supplementary material C summarizes the details of each of the NTCP models.

NTCP calculations

The PBT and XRT-plans were transferred to MIM maestro ver. 7.0 (MIM Software, Cleveland, OH, USA) and dose-volume histogram (DVH) data of the normal liver dose was extracted. To convert to the normalized biologic effective dose from the original physical doses, the parameters shown in Supplementary material C were used for the dose per fraction and the α/β ratio in each NTCP model. To determine the NTCP value, the biological effective dose was fitted to the respective NTCP model. Details of the NTCP calculations were described in original reports [22–25]. The NTCP value was calculated by the appropriate model proposed based on the Child-Pugh or ALBI grade of the case.

The ΔNTCP is a reference value for the relative advantage of the PBT when compared to XRT. To obtain the value for ΔNTCP with PBT and XRT-plans, the following equation was used.

$$\Delta NTCP = NTCP_{XRT-plan} - NTCP_{PBT-plan}$$

As for the threshold of ΔNTCP for differences in adverse events, we used the thresholds proposed by Langendijk et al. [10]. In that article, the thresholds of ΔNTCP for grades 2, 3, and ≥ 4 were set at 10%, 5%, and 2%, respectively. Therefore, we used a threshold of 5% for the models of Dawson, Cheng, and Xu. In setting appropriate thresholds for the Pursely model, a threshold of 5% was adopted because changes in these values can significantly influence subsequent treatment decisions.

Statistical analysis

The NTCP models used in this study were specified by the values for the normalized healthy liver dose. Therefore, a logistic regression analysis was performed for the total tumor diameter (the sum for the target tumors), normal liver volume, number of tumors, and localization of the tumors (hilum or other locations), which potentially affect the liver dose. As for tumor location, the hepatic hilum was defined as within 20 mm of the main stem or first branch of the portal vein. If at least one of the lesions was in the hilar region, it was considered to have hilar involvement. Statistical significance was defined as a p-value of <0.05 and a 95% confidence interval of the odds ratio not including 1 [26]. The statistical analysis was performed with the JMP version 16 (SAS, Cary, NC).

Results

Fig. 1 shows the dose-volume histograms of normal liver volume by dose-prescription. The PBT-plan has advantages in sparing the parts of liver receiving low doses. Fig. 2 shows the details of NTCP or ΔNTCP values for each model. The overall NTCP distribution varies by model, but patients in each model can be divided in groups of ΔNTCP $<$ 5% or ≥ 5%. The number of cases with ΔNTCP ≥ 5% in each model was six (15%) in the Dawson model, four (10%) in Cheng, 12 (30%) in Xu, 26 (65%) in Pursley with the endpoint of CP score increase ≥ 2, and 22 (55%) in Pursley with ALBI grade increase ≥ 1.

The results of the logistic regression analysis are shown in Table 3. The identified factors predicting the benefit of PBT differed among the NTCP models. In four of five NTCP models, the total tumor diameter was a significant factor ($p < 0.01$) for indicating benefits of PBT. In the two Pursley models, the number of tumors (1 vs 2) and tumor location (hilum or others) were also significant ($p < 0.01$). Different from this, the normal liver volume was not significant in any of the five models.

Fig. 3 shows two representative cases. Case 1 is a tumor at the peripheral part and case 2 is with multiple lesions at the hepatic hilum. Although each of the tumor diameters is smaller in case 2, the ΔNTCP value suggests that the benefit of PBT is greater in this case.

Discussion

Model-based selection has been proposed as a useful method in selecting cases with superior benefits by PBT for primary liver tumors and this method has already been applied clinically in the field of head and neck cancers [27]. Although model-based selection should be useful, it may be limited to promote the workflow in all cases due to time or personnel constraints. To evaluate which cases could benefit most, it would be desirable to make decisions based on the factors that affect the dose distributions in PBT and XRT-plans. Our study showed that advantages of PBT could be predicted by the following factors: total tumor diameter, tumor location, and the number of tumors. Although the factors considered here are not sufficient for clinical decision making, further development of this study will show some cases predicting benefits of PBT without a treatment plan.

In future clinical trials, much caution is needed for hepatic toxicity analysis of differences between PBT and XRT. Cheng et al. and Sanford et al. compared patients who undergo PBT or XRT for liver tumors, retrospectively, and reported improved survival and lower adverse event incidence with PBT [7,8]. Their studies are important in showing the benefits of PBT, however, the patients included in both studies had not been stratified by factors influencing liver doses. For example, a tumor located in the periphery of the liver have very limited benefit from PBT, even if the tumor diameter is nearly 40 mm (Fig. 3). These cases would be expected to show no difference in the risk of hepatic toxicity at the time of treatment planning. Widder et al. pointed out that the inclusion of such cases with no potential benefit of PBT may make

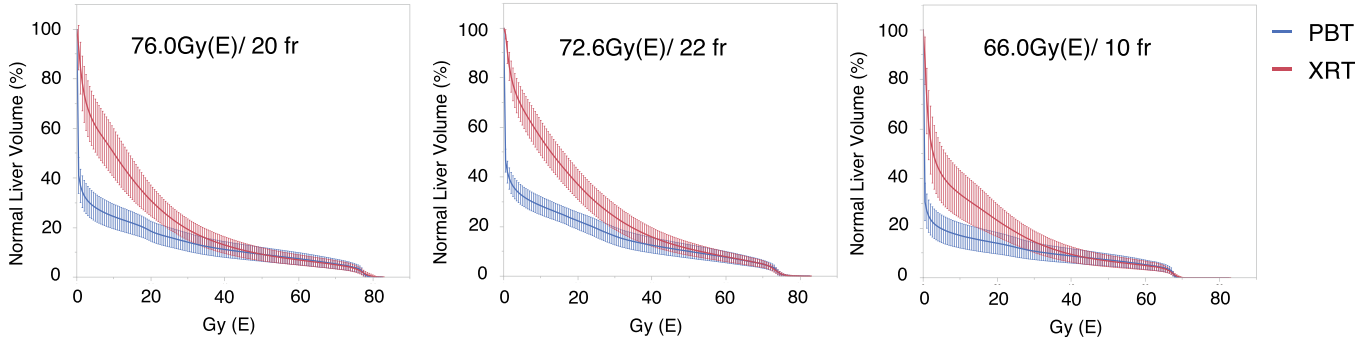


Fig. 1. Dose-volume histograms of normal livers (Liver – GTV) with 95% confidence intervals in patient group pre prescription dose. GTV: gross tumor volume.

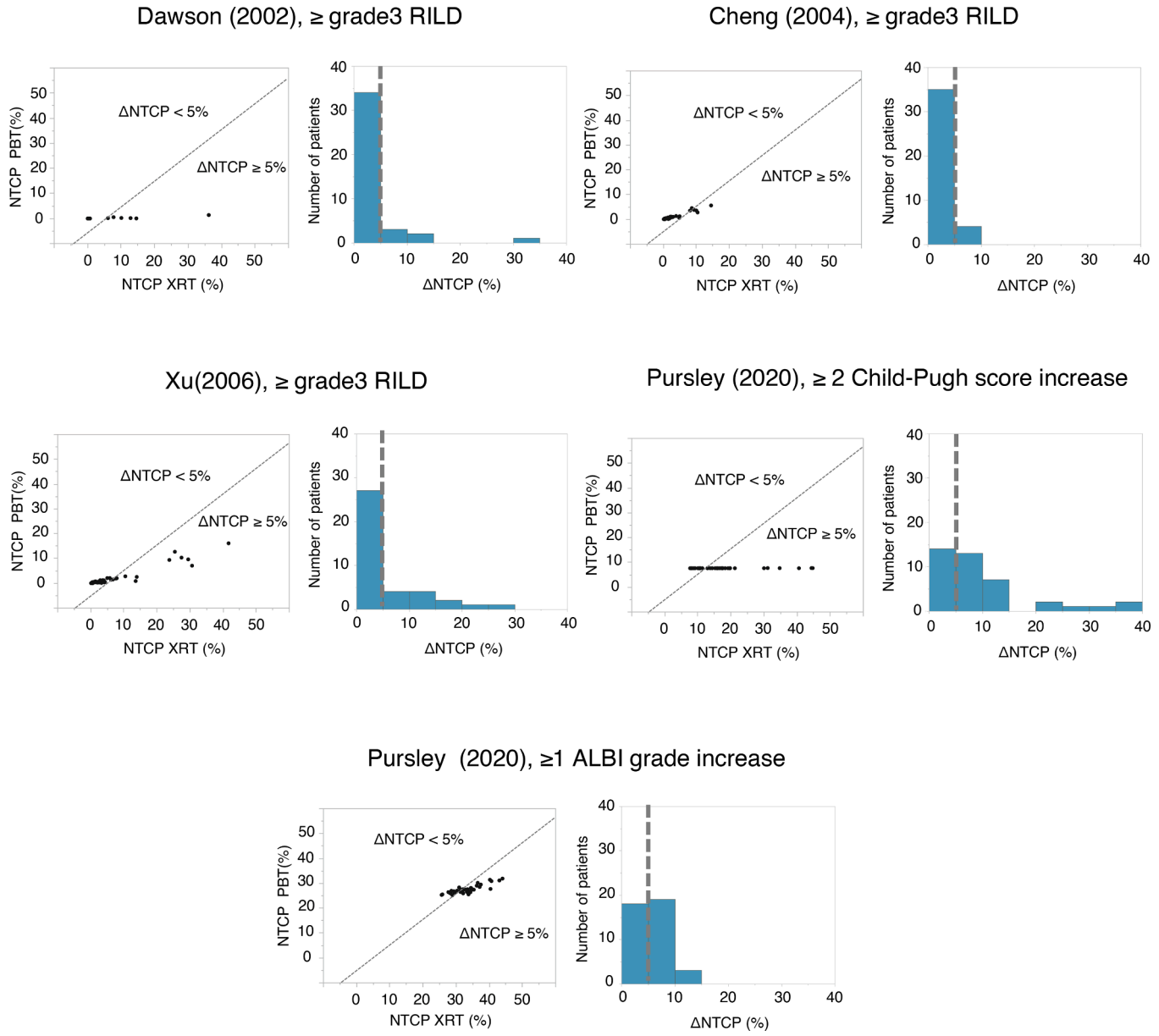


Fig. 2. The NTCP values in the PBT and XRT-plans (left panels, shown with dots) and the distribution of ΔNTCP (right panels, shown with blue bars). The dotted line indicates the threshold values (5%) of ΔNTCP in the models. ALBI: albumin-bilirubin, NTCP: normal tissue complication probability, PBT: proton beam therapy, RILD: radiation-induced liver disease, XRT: X-ray therapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the interpretation of the results obtained difficult [11]. One challenge in future clinical trials is how to evaluate these non-beneficial cases.

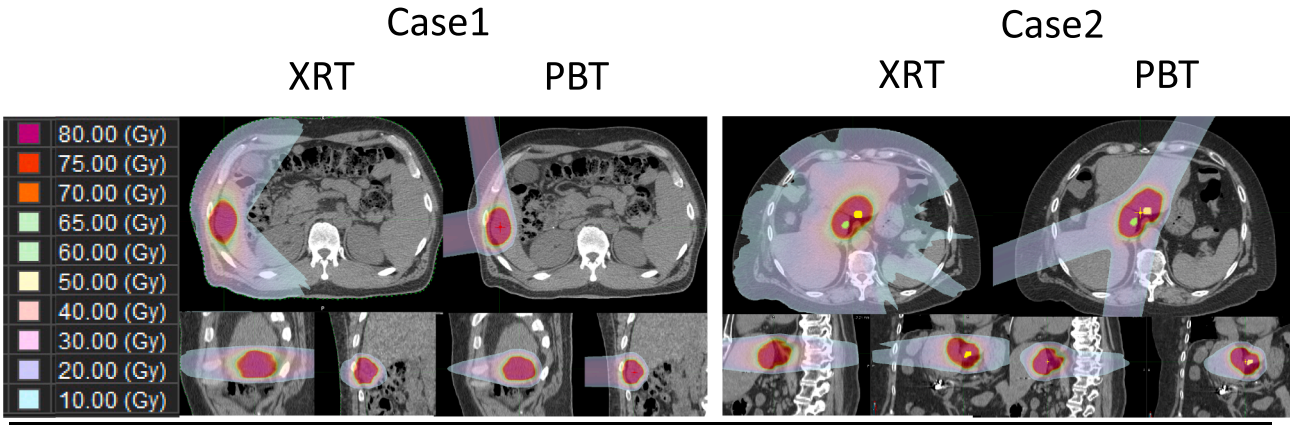
Although there have been studies comparing XRT and PBT plans in liver tumors, the issue remains as to which NTCP model to use. Mondlane et al. performed a study with planning comparisons using ten patients with metastatic liver tumors [16]. Toramatsu et al. also compared dosimetric parameters of ten liver tumors from 3.4 to 16.1 cm with PBT and intensity-modulated radiotherapy (IMRT) [15]. While these studies are promising in showing the possibility to select cases benefitting with PBT, both studies estimated NTCP values using only the Dawson model. As shown in Fig. 2, the values of NTCP are various among models even for the same case. Therefore, physicians need to be fully aware of the possibility that the results can be different depending on the selected NTCP model.

In this present study, the significant factors affecting case selection differed depending on the NTCP model in CP grade A cases. The Dawson, Xu, and Cheng model were associated with total tumor diameter. In the two Pursley models, however, the results were different. In the original article, Pursley et al. reported that the low dose region (5–10 Gy) in the liver was strongly associated with a CP score or ALBI grade increase [25]. From our DVH comparison, an advantage of PBT is clearly that it gives the normal liver volume low doses (Fig. 1). This result is similar to previous planning studies [15,16]. The extent of the low-dose region becomes more apparent with XRT when treating multiple lesions at the hepatic hilum, as shown Fig. 3. Considering these results, the Pursley model may be appropriate in terms of estimating the benefits of reducing the low-dose region, which is an advantage of PBT. For a more appropriate model-based selection, the solution may be to combine multiple NTCP models. There is also a report with an attempt to set an optimal threshold value when using multiple NTCP models with different endpoints [10]. More studies are needed on which NTCP model to use and how to combine models for model-based selection.

Table 3
Logistic regression analysis.

Model	Liver status	Endpoint	n	Factor	Odds ratio (95% CI)	P value
Dawson (2002)	Not considered	≥ grade3 RILD	40	Total tumor diameter (cm)	6.56 (1.79 – 89.52)	0.001
				Number (1 vs 2)	3.95 (0.04–2348.87)	0.571
				Location (hilum vs others)	42.68 (0.60–727194.74)	0.100
				Normal liver volume (cm^3)	0.79 (0.45–1.25)	0.337
Cheng (2004)	For CP grade A	≥ grade3 RILD	40	Total tumor diameter (cm)	5.99 (1.44 – 83.83)	0.007
				Number (1 vs 2)	2.77 (0.04 – 1071.60)	0.648
				Location (hilum vs others)	2.86 (0.08 – 493.76)	0.576
				Normal liver volume (cm^3)	0.95 (0.58–1.47)	0.836
Xu (2006)	For CP grade A	≥ grade3 RILD	40	Total tumor diameter (cm)	9.94 (3.02 – 75.12)	<0.001
				Number (1 vs 2)	2.20 (0.05 – 199.93)	0.695
				Location (hilum vs others)	3.46 (0.31 – 71.88)	0.316
				Normal liver volume (cm^3)	0.76 (0.47–1.05)	0.113
Pursely (2020)	For CP grade A	CP score ≥ 2+	40	Total tumor diameter (cm)	3.44 (0.75 – 15.69)	0.043
				Number (1 vs 2)	75.22 (1.63 – 3463.13)	0.003
				Location (hilum vs others)	23.97 (2.26 – 253.30)	0.001
				Normal liver volume (cm^3)	0.69 (0.45 – 1.07)	0.047
	For ALBI grade 1 or 2	ALBI grade ≥ 1+	40	Total tumor diameter (cm)	3.01 (1.26 – 10.27)	0.009
				Number (1 vs 2)	13.41 (1.43 – 244.51)	0.020
				Location (hilum vs others)	8.30 (1.44 – 72.23)	0.016
				Normal liver volume (cm^3)	0.89 (0.65 – 1.14)	0.375

Total tumor diameter (cm) and liver volume (per 100-cm^3 increase) were set as a continuous variable. ALBI: albumin-bilirubin, CP grade: Child-Pugh grade, CI: confidence interval, RILD: radiation-induced liver disease



Case detail	Case 1: Peripheral tumor	Case 2: Multiple tumors at hilum
Location, Diameter	Segment 6: 38 mm	Segment 1: 9mm Segment 2: 5mm
Normal liver volume	1503.5 cm^3	2164.4 cm^3
Child-Pugh / ALBI grade	A/ 1	A/ 1
Dose/ Fractions	76Gy(E)/ 20fr	76Gy(E)/ 20fr
Model	ΔNTCP(%)	
Dawson (2002)	< 0.1	< 0.1
Cheng (2004)	< 0.1	1.5
Xu (2006)	< 0.1	3.7
Pursley (2020) (≥ 2 CP score increase)	< 0.1	12.1
Pursley (2020) (≥ 1 ALBI grade increase)	0.3	7.8

Fig. 3. Cases of the XRT and PBT-plans. ALBI: albumin-bilirubin, NTCP: normal tissue complication probability; PBT: proton beam therapy; XRT: X-ray therapy.

Some of the limitations of this study are as follows. The present study was conducted to investigate hepatic toxicity in patients with Child-Pugh grade A, with a maximum tumor diameter of ≤ 5 cm. The results of this study show a need to investigate more diverse cohorts of liver tumors receiving proton or photon therapy. In addition, the NTCP value may be influenced by the difference in planning volume between XRT and PBT. For example, in the PBT-plan of case 2 (Fig. 3), the margins of 5–8 mm are given for the proximal and distal directions as the range uncertainties (beam range of 3.5%+1mm). Therefore, the planning volume would be larger than with XRT, which may affect the NTCP value calculated by the normal liver volume (Liver-GTV). Another limitation is the differences in plan optimization methods. The PBT-plan was robustly optimized, but XRT was PTV based in this study. Korevaar et al. reported a practical approach to robustness evaluation for PTV-less photon and proton treatment toward model-based selection [28]. Miura et al. studied the robust optimization of VMAT for liver cancer and they concluded that it could be feasible [29]. Compared to XRT, PBT is known to be less robust in the patient setup and motion, which may deteriorate the target dose. In clinical practice, management of intra/ inter-fractional variations in PBT need to be carefully considered to deliver the planned target dose and ensure the NTCP superiority.

Conclusions

The total tumor diameter, tumor location, and number of tumors were important factors to predict benefits of PBT in CP grade A. These factors may allow us to predict the benefits of PBT in advance.

Declaration of Competing Interest

K.K. is an employee of the research institute of Hitachi, Ltd., currently working for Hokkaido University under a secondment agreement. K.K. declares that this research has no relationship to Hitachi, Ltd. All other authors declare that they have no conflicts of interest to declare.

Acknowledgement

This research is supported by JSPS KAKENHI Grant Number JP16K10379 and the Akiyama Memorial Foundation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2022.05.004.

References

[1] Feng M, Suresh K, Schipper MJ, Bazzi L, Ben-Josef E, Matuszak MM, et al. Individualized Adaptive Stereotactic Body Radiotherapy for Liver Tumors in Patients at High Risk for Liver Damage: A Phase 2 Clinical Trial. JAMA Oncol 2018;4(1):40.
[2] Teraoka Y, Kimura T, Aikata H, Daijo K, Osawa M, Honda F, et al. Clinical outcomes of stereotactic body radiotherapy for elderly patients with hepatocellular carcinoma. Hepatol Res 2018;48(2):193–204.
[3] Jeong Y, Jung J, Cho B, Kwak J, Jeong C, Kim JH, et al. Stereotactic body radiation therapy using a respiratory-gated volumetric-modulated arc therapy technique for small hepatocellular carcinoma. BMC Cancer 2018;18(1).
[4] Sun J, Zhang T, Wang J, Li W, Zhang A, He W, et al. Biologically effective dose (BED) of stereotactic body radiation therapy (SBRT) was an important factor of therapeutic efficacy in patients with hepatocellular carcinoma (≤5 cm). BMC Cancer 2019;19:846.
[5] Uchinami Y, Katoh N, Abo D, Taguchi H, Yasuda K, Nishioka K, et al. Treatment outcomes of stereotactic body radiation therapy using a real-time tumor-tracking radiotherapy system for hepatocellular carcinomas. Hepatol Res 2021;51(8):870–9.
[6] Chadha AS, Gunther JR, Hsieh C-E, Aliru M, Mahadevan LS, Venkatesulu BP, et al. Proton beam therapy outcomes for localized unresectable hepatocellular carcinoma. Radiother Oncol 2019;133:54–61.
[7] Cheng J-Y, Liu C-M, Wang Y-M, Hsu H-C, Huang E-Y, Huang T-T, et al. Proton versus photon radiotherapy for primary hepatocellular carcinoma: a propensity-matched analysis. Radiat Oncol 2020;15(1).
[8] Sanford NN, Pursley J, Noe B, Yeap BY, Goyal L, Clark JW, et al. Protons vs Photons for Unresectable Hepatocellular Carcinoma: Liver Decompensation and Overall Survival Proton Radiotherapy for Hepatocellular Carcinoma. Int J Radiat Oncol Biol Phys 2019;105:64–72.
[9] Hasan S, Abel S, Verma V, Webster P, Arscott WT, Wegner RE, et al. Proton beam therapy versus stereotactic body radiotherapy for hepatocellular carcinoma: practice patterns, outcomes, and the effect of biologically effective dose escalation. J Gastrointest Oncol 2019;10(5):999–1009.
[10] Langendijk JA, Boersma LJ, Rasch CRN, van Vulpen M, Reitsma JB, van der Schaaf A, et al. Clinical Trial Strategies to Compare Protons With Photons. Semin Radiat Oncol 2018;28(2):79–87.
[11] Widder J, van der Schaaf A, Lambin P, Marijnen CAM, Pignol J-P, 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(1):30–6.
[12] 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(3):267–73.
[13] McNamara AL, Hall DC, Shusharina N, Liu A, Wei X, Ajdari A, et al. Perspectives on the model-based approach to proton therapy trials: A retrospective study of a lung cancer randomized trial. Radiother Oncol 2020;147:8–14.
[14] Dutz A, Lühr A, Troost EGC, Agolli L, Bütof R, Valentini C, et al. Identification of patient benefit from proton beam therapy in brain tumour patients based on dosimetric and NTCP analyses. Radiother Oncol 2021;160:69–77.
[15] 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. Radiation Oncology 2013;8(1).
[16] Mondlane G, Ureba A, Gubanski M, Lind PA, Siegbahn A. Estimation of the risk for radiation-induced liver disease following photon- or proton-beam radiosurgery of liver metastases. Radiation Oncology 2018;13:206.
[17] Shimizu S, Miyamoto N, Matsuura T, Fujii Y, Umezawa M, Umegaki K, et al. A proton beam therapy system dedicated to spot-scanning increases accuracy with moving tumors by real-time imaging and gating and reduces equipment size. PLoS ONE 2014;9(4):e94971.
[18] Vanderstraeten B, Goddeeris B, Vandecasteele K, van Eijkeren M, De Wagter C, Lievens Y. Automated instead of manual treatment planning? A plan comparison based on dose-volume statistics and clinical preference. Int J Radiat Oncol Biol Phys 2018;102(2):443–50.
[19] McConnell KA, Marston T, Zehren BE, Lirani A, Stanley DN, Bishop A, et al. Dosimetric Evaluation of Pinnacle's Automated Treatment Planning Software to Manually Planned Treatments. Technol Cancer Res Treat. 2018;17:1533033818780064.
[20] Gallio E, Giglioli FR, Girardi A, Guarneri A, Ricardi U, Ropolo R, et al. Evaluation of a commercial automatic treatment planning system for liver stereotactic body radiation therapy treatments. Physica Med 2018;46:153–9.
[21] Zhang Y, Li T, Xiao H, Ji W, Guo M, Zeng Z, et al. A knowledge-based approach to automated planning for hepatocellular carcinoma. J Appl Clin Med Phys 2018;19(1):50–9.
[22] Dawson LA, Normolle D, Balter JM, McGinn CJ, Lawrence TS, Ten Haken RK. Analysis of radiation-induced liver disease using the Lyman NTCP model. Radiat Oncol Biol 2002;53(4):810–21.
[23] Cheng J-H, Wu J-K, Lee P-T, Liu H-S, Jian J-M, Lin Y-M, et al. Biologic susceptibility of hepatocellular carcinoma patients treated with radiotherapy to radiation-induced liver disease. Int J Radiat Oncol Biol Phys 2004;60(5):1502–9.
[24] Xu Z-Y, Liang S-X, Zhu Ji, Zhu X-D, Zhao J-D, Lu H-J, 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(1):189–95.
[25] Pursley J, El Naqa I, Sanford NN, Noe B, Wo JY, Eyler CE, et al. Dosimetric Analysis and Normal-Tissue Complication Probability Modeling of Child-Pugh Score and Albumin-Bilirubin Grade Increase After Hepatic Irradiation. Int J Radiat Oncol Biol Phys 2020;107(5):986–95.
[26] Hopkins ZH, Moreno C, Secrest AM. Lack of confidence interval reporting in dermatology: a call to action. Br J Dermatol 2019;180(4):910–5.
[27] Tambas M, Steenbakkers RJHM, van der Laan HP, Wolters AM, Kierkels RGJ, Scandurra D, et al. First experience with model-based selection of head and neck cancer patients for proton therapy. Radiother Oncol 2020;151:206–13.
[28] Korevaar EW, Habraken SJM, Scandurra D, Kierkels RGJ, Unipan M, Eenink MGC, et al. Practical robustness evaluation in radiotherapy – A photon and proton-proof alternative to PTV-based plan evaluation. Radiother Oncol 2019;141:267–74.
[29] Miura H, Ozawa S, Kusaba H, Doi Y, Kenjo M, Yamada K, et al. Characterization of robust optimization for VMAT plan for liver cancer. Rep Pract Oncol Radiother 2020;25(3):376–81.