Original Article

Correlation between Biological Effective Dose and Radiation-induced Liver Disease from Hypofractionated Radiotherapy

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Abstract

Background: The prevention of radiation-induced liver disease (RILD) is very significant in ensuring a safe radiation treatment and high quality of life. **Aims and Objectives:** The purpose of this study is to investigate the correlation of physical and biological effective dose (BED) metrics with liver toxicity from hypo-fractionated liver radiotherapy. **Materials and Methods:** 41 hypo-fractionated patients in 2 groups were evaluated for classic radiation-induced liver disease (RILD) and chronic RILD, respectively. Patients were graded for effective toxicity (post-treatment minus pre-treatment) using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Physical dose (PD) distributions were converted to BED. The V_{10Gy}, V_{15Gy}, V_{20Gy}, V_{25Gy} and V_{30Gy} physical dose-volume metrics were used in the analysis together with their respective BED-converted metrics of $V_{16.7Gy3}$, V_{30Gy3}, $V_{46.7Gy3}$, $V_{66.7Gy3}$ and V_{90Gy3}. All levels were normalized to their respective patient normal liver volumes (NLV) and evaluated for correlation to RILD. Results were measured quantitatively using R^2 regression analysis. **Results:** The classic RILD group had median follow-up time of 1.9 months and the average PD-NLV normalized V_{10Gy}, V_{15Gy}, V_{20Gy}, V_{25Gy} and V_{30Gy} metrics per grade were plotted against RILD yielding R^2 correlations of 0.84, 0.72, 0.73, 0.65 and 0.70, respectively while the BED-volume metrics of $V_{16.7Gy3}$, V_{30Gy3}, $V_{46.7Gy3}$, $V_{66.7Gy3}$ and V_{90Gy3} resulted in correlation values of 0.84, 0.74, 0.66, 0.78 and 0.74, respectively. BED compared to PD showed a statistically significant (p=.03) increase in R^2 for the classic RILD group. Chronic RILD group had median follow-up time of 12.3 months and the average PD-NLV normalized V_{10Gy}, V_{15Gy}, V_{20Gy}, V_{25Gy} and V_{30Gy} metrics per grade were plotted against RILD grade yielding R^2 correlations of 0.48, 0.92, 0.88, 0.90 and 0.99 while the BED-volume metrics of $V_{16.7Gy3}$, V_{30Gy3}, $V_{46.7Gy3}$, $V_{66.7Gy3}$ and V_{90Gy3} resulted in correlation values of 0.43, 0.94, 0.99, 0.21 and 0.00, respectively. **Conclusion:** The strong correlations of the V_{10Gy} and V_{15Gy} PD-volume metrics as well as the $V_{16.7Gy3}$ (BED of V_{10Gy}) to both classic and chronic RILD imply the appropriateness of the current 15_{Gy} evaluation level for liver toxicity with hypo-fractionated treatments.

Keywords: Biological effective dose, Common Terminology Criteria for Adverse Events, hypofractionated, radiation-induced liver disease, stereotactic body radiation therapy, toxicity analysis

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Introduction

In the modern-era clinic, the delivery of stereotactic body radiation therapy (SBRT) and hypofractionated treatments has become a commonplace in the management of primary[1] and metastatic liver tumors[2,3] with proven effectiveness in providing high local control rates.[4] The advancement of SBRT allows the precise delivery of high doses of radiation to targets while minimizing dose to surrounding critical structures. The central concern, however, is the possibility of radiation toxicity to the liver which in some cases can prove fatal.[5-7] This serves as a dose-limiting factor in the delivery of hypofractionated treatments.

As a consequence, the prevention of radiation-induced liver disease (RILD) becomes of paramount importance in ensuring

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a commendable standard of patient care, allowing safe radiation treatment and high quality of life. The use of the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 allows the assessment of presence and magnitude of radiation-associated effects.[8] This assessment, however, becomes increasingly difficult with the use of hypofractionated treatments. The presently available data are limited to extrapolated toxicity from standard fractionated treatments and so the investigation of the relationship between RILD and absorbed dose becomes necessary.[1,9]

Typically, RILD occurs 4–8 weeks after termination of RT, but sometimes, it has occurred as early as 2 weeks or as late as 7 months post-RT.[10] A broad range of RILD incidence rates (~6%–66%) has been reported in the literature for hepatic radiation of 30–35 Gy. There are two types of RILD: classic RILD and nonclassic RILD. Patients with classic RILD usually have symptoms of fatigue, abdominal pain, increased abdominal girth, hepatomegaly, and anicteric ascites 0.5–4 months after liver RT, whereas patients who develop chronic RILD have underlying chronic hepatic diseases, such as cirrhosis and viral hepatitis, and show more dysregulated hepatic functions after 6 months post-RT.[5]

This issue is further complicated by the differing biological effects with varying fraction sizes.[11-23] However, the adoption of the linear-quadratic linear (LQ-L) biological effective dose (BED) formulation[24] for this study provides a basis, for which varying low and high dose per fraction treatments can be analyzed. This manuscript aims at determining the correlation of physical and BED dose metrics from hypofractionated treatments with liver toxicity as expressed by RILD. This information can be a very valuable input during treatment plan optimization where much of the effort is devoted to the reduction or even elimination of potential complications to the organs at risk.

Materials and Methods

A total of 41 patients, who reported RILD, were enrolled in this study. The patient cohort was split into two subgroups according to time that they developed RILD ($t_{follow\text{-}up}$). In this way, they could be listed in the respective classic or chronic RILD groups. Thirty-six patients received an intensity-modulated radiation therapy (IMRT) course of 3 Gy in 8–10 fx (24–30 Gy) while five patients received intensity-modulated SBRT, three receiving 10 Gy in 5 fx (50 Gy), and two receiving 15 Gy in 3 fx (45 Gy). Group one, which corresponds to the classic RILD with $t_{follow\text{-}up}$ <4 months, consisted of 25 patients (23 IMRT and 2 SBRT), whereas group two, which corresponds to the chronic RILD with $t_{follow\text{-}up}$ >6 months consisted of 16 patients (13 IMRT and 3 SBRT). Patient's PD distributions were exported and converted to BED values using a constructed MATLAB 2010b (MathWorks, Boston, MA) graphical user interface conversion application. Conversions were made using the linear quadratic (LQ) model for doses <6 Gy per fraction and LQ-L model[22] for doses per fraction ≥6 Gy, which can be written as:

$$BED_n = D + [D^2/(\alpha/\beta)] \text{ for } D < D_T \quad (1)$$

and

$$BED_n = D_T + [D_T{}^2/(\alpha/\beta)] + [(\gamma/\alpha)(D - D_T)] \text{ for } D \geq D_T \quad (2)$$

with

$$\gamma/\alpha = 1 + [2D_T/(\alpha/\beta)] \quad (3)$$

where BED is the biological effective dose, *n* is the number of fractions, D is the dose per fraction, α/β is the point at which the linear and quadratic components of cell killing are equal, D_T is the threshold dose for which the LQ model converts to the LQ-L model, and γ is the natural log cell kill per Gy in the high dose per fraction linear portion of the survival curve. Values of $\alpha/\beta = 3$ Gy, $D_T = 6$ Gy, $n = 3$, 5, and 10 fractions were used. γ/α was approximated using the slope of the line tangent to the LQ curve at the point $D_T = 6$ Gy as done in Astrahan.[24] The tangent line, γ/α, expressed by the derivative reduces to 5 as follows: $\gamma/\alpha = 1 + 2D_T/(\alpha/\beta) = 1 + 2^*$ (6 Gy/3 Gy) = 5.

This model was chosen due to the deviation of the LQ formulation prediction and experimental observations in many clonogenic cell-survival studies showing a dose–response relationship exhibiting an exponential decrease of survival at high dose which more closely approximates a straight line on a log-linear plot.[12,13,19,25-27] Specifically, in the paper by Astrahan,[24] the survival response curves of a number of different tissues are presented as part of a very comprehensive analysis about the LQ and LQ-L models and the transition from one model to the other. The use of the exact value of 6 Gy is not critical in our study because the fractional doses of the SBRT cases are much higher than that of 10 and 15 Gy.

The patients were graded by a physician using the CTCAE v4.0.[8] Patients' pretreatment (initial) and posttreatment (follow-up) RILD grades were recorded. The effective RILD score was determined by the difference of those grades (follow-up grade minus initial grade). The normal liver volume (NLV) was defined as the total liver volume (TLV) minus the gross tumor volume (GTV).[28]

$$NLV = TLV - GTV \quad (4)$$

The mean physical dose (PD) together with the $V_{10Gy,}$ $V_{15Gy,}$ $V_{20Gy,}$ V_{25Gy}, and V_{30Gy} dose–volumes metrics to the NLV was calculated along with their respective BED values of $V_{16.7Gy3,}$ $V_{30Gy3,}$ $V_{46.7Gy3,}$ $V_{66.7Gy3}$, and V_{90Gy3}. The above dose–volumes were normalized for each patient by division by that patient's NLV. Based on the values of those parameters, the value of the averaged volume corrected dose ($\overline{VCD}$) could be calculated by the following mathematical expression:

$$\overline{VCD} = \frac{1}{N_{RILD}} \sum_{i=0}^{N_{RILD}} \frac{V_{X,i}}{NLV_i} \quad (5)$$

where $V_{X,i}$ is the liver volume of the ith patient receiving at least X dose; NLV_i is the NLV of the ith patient; and N_{RILD} is the number of patients in the RILD grade category (acute or chromic).

The $\overline{VCD}$ (Equation 5) was graphed against the effective RILD grade and evaluated via R-squared linear regression fitting to quantitatively determine the correlation between effective RILD grade, PD, and BED. Box-and-whisker plots

were created to show the spread and distribution of averaged dose–volume fractions within each RILD grade.

Results

The mean PD and corresponding BED values of all the patients examined in this study are shown in Table 1 for the classic and chronic RILD, respectively.

$\%\overline{VCD}$ for classic and chronic RILD is shown in Table 2. The classic RILD group had a median follow-up time of 1.9 months with the physical $\overline{VCD}$ for V_{10Gy}, V_{15Gy}, V_{20Gy}, V_{25Gy}, and V_{30Gy} per grade plotted against RILD yielding R^2 correlations of 0.84, 0.72, 0.73, 0.65, and 0.70, respectively. The corresponding biological $\overline{VCDs}$ of $V_{16.7Gy3}$, V_{30Gy3}, $V_{46.7Gy3}$, $V_{66.7Gy3}$, and V_{90Gy3} resulted in R^2 correlations of 0.84, 0.74, 0.66, 0.78, and 0.74, respectively.

The chronic RILD group had a median follow-up time of 12.3 months with the physical $\overline{VCD}$ for V_{10Gy}, V_{15Gy}, V_{20Gy}, V_{25Gy}, and V_{30Gy} per grade plotted against RILD grade yielding R^2 correlations of 0.48, 0.92, 0.88, 0.90, and 0.99 while biological $\overline{VCDs}$ of $V_{16.7Gy3}$, V_{30Gy3}, $V_{46.7Gy3}$, $V_{66.7Gy3}$, and V_{90Gy3} resulted in R^2 correlations of 0.43, 0.94, 0.99, 0.21, and 0.00, respectively. Linear regression analysis is shown in Figure 1.

Table 1: Individual mean physical dose and corresponding biological effective dose values for the classic and chronic radiation-induced liver disease patient subgroups

Patient #	Classic RILD		Chronic RILD	
	Mean PD (Gy)	Mean BED (Gy)	Mean PD (Gy)	Mean BED (Gy)
1	12.85	21.9	6.0	9.1
2	7.72	12.5	15.0	25.8
3	11.62	20.2	10.6	17.4
4	13.58	22	4.8	7.2
5	7.07	10.4	10.8	18.0
6	7.35	11.5	7.9	11.7
7	11.57	19.4	10.8	4.3
8	11.21	18.0	11.5	38.1
9	15.02	26.9	11.5	19.0
10	7.94	11.8	5.0	7.2
11	8.70	15.4	1.7	2.8
12	4.86	6.7	7.1	11.6
13	8.39	12.7	2.8	4.2
14	8.17	14.3	7.2	11.8
15	4.00	5.7	11.5	19.5
16	16.34	27.7	1.6	2.1
17	10.05	16.1		
18	21.50	39.8		
19	7.57	12.5		
20	15.28	25.7		
21	16.93	29.0		
22	5.38	8.6		
23	12.00	19.4		
24	21.0	62.9		
25	4.9	13.1		

PD: Physical dose, BED: Biological effective dose, RILD: Radiation-induced liver disease

The two closest correlated dose–volume levels of averaged PD and BED for both classic and chronic RILD were further analyzed by creation of box-and-whisker plots to display the distribution of data. This corresponded to V_{10Gy}, V_{20Gy} PD–volumes and $V_{16.7Gy3}$, $V_{66.7Gy3}$ BED–volumes for classic RILD which can be seen in Figure 2. For chronic RILD, this corresponded to the V_{15Gy}, V_{30Gy} PD–volumes and with BED–volumes of V_{30Gy3}, $V_{46.7Gy3}$ whose spread can be seen in Figure 3.

Discussion

Ideally, balanced groups between IMRT and SBRT were planned to be used for this study. However, it was difficult to enroll patients and consistently collect clinical data for the SBRT arm of the study. Nevertheless, the scope of the study was not to compare the clinical effectiveness of IMRT vs. SBRT, but to identify the existence of correlations between dose–volume metrics with RILD. To accomplish our goal, we had to convert all the dose distributions to an equivalent fractionation scheme of 2 Gy fractional dose because fraction size has long since been known to be a dominant factor for toxicity risk.[29] The hypofractionation trend of increasing dose per fraction has shown clear evidence of increased local tumor control rates, however with an existing caveat of larger toxicity potential. In the case of the liver, the most severe effect is characterized as RILD which has been reported as one of the most serious treatment-related complications for patients with hepatic irradiation.[30]

The accuracy and validity of the liver PD constraint is questionable when delivering large doses per fraction to high total doses as is done in hypofractionation and especially SBRT.[11,23] Table 3 highlights the current dose constraints for hypofractionated partial-liver radiotherapy as recommended by the quantitative analysis of normal tissue effects in the clinic (QUANTEC) group for radiation-associated liver injury.[31] One of the particular interests is the preservation of ≥700 mL of normal liver to receive a dose of ≤15 Gy. The use of this safety criterion has, to the date of the QUANTEC publication (2010), resulted in zero RILD or severe toxicity following SBRT.[32] While a serious complication rate of zero is applauded, this fact implies the restriction of potential improvements on overall survival rates attainable with dose escalation due to an overconservative dose–volume constraint.

From Figures 2 and 3, we observe that very strong positive correlations ($R^2 = 0.70$–0.99) exist with the lower dose levels of V_{10Gy} and V_{15Gy} for both classic and chronic RILD, corresponding to their biological equivalents of $V_{16.7Gy3}$ and V_{30Gy3}, where we also observe strong correlations. Furthermore, it is noteworthy to mention the near-equal correlations between PD and its respective BED in both RILD categories. Although the final results indicate that the PDs and their respective BED correlate with RILD very similarly, this is something that was not known

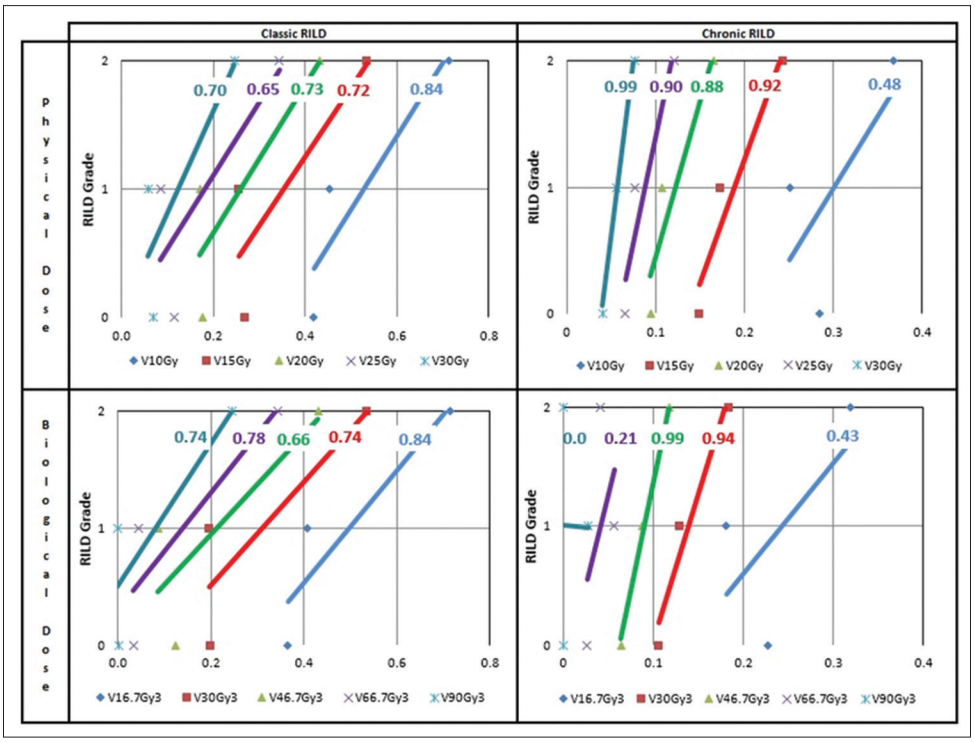

Figure 1: Averaged physical and biological dose–volumes per grade plotted against classic and chronic radiation-induced liver disease with the regression values also shown

Table 2: Percent volume corrected dose averages for classic ($t_{follow-up}$ <4 months) and chronic ($t_{follow-up}$ >6 months) radiation-induced liver disease

	V_{10Gy}	V_{15Gy}	V_{20Gy}	V_{25Gy}	V_{30Gy}	$V_{16.7Gy3}$	V_{30Gy3}	$V_{46.7Gy3}$	$V_{66.7Gy3}$	V_{90Gy3}	*n*
Classic	43.3	27.8	18.8	12.3	7.6	38.4	21.3	13.3	4.7	1.2	25
Chronic	29.5	18.0	11.6	8.3	5.4	23.6	13.2	8.5	4.0	0.9	16
P	<0.05	<0.05	<0.05	0.13	0.22	<0.05	<0.05	0.11	0.71	0.87	

V_d: Volume encompassing the d (Gy physical or Gy_3 biological) dose level

Table 3: Current hypofractionated partial-liver radiotherapy dose-constraints as recommended by the quantitative analysis of normal tissue effects in the clinic group for radiation-induced liver injury

WLRT	RLRT	SBRT
≤30 Gy at 2 Gy/fx 21 Gy in 7 fx	<32 Gy at 2 Gy/fx >10% of normal liver spared	<15 Gy in 3 fx <20 Gy in 6 fx ≥700 cc of normal liver receiving ≤15 Gy 3-5 fx

Gy/fx: Gray per fraction, fx: Fraction, RT: Radiotherapy, RLRT: Partial-liver RT, QUANTEC: Quantitative analysis of normal tissue effects in the clinic, SBRT: Stereotactic body RT, WLRT: Whole liver RT

at the beginning of this work. However, as a finding of this study, it is very interesting and it has significant clinical implications because it indicates that the PD constraints can be used during treatment plan optimization to reduce the risk for RILD post-RT.

It is very interesting to compare the present findings with results based on high dose rate (HDR) brachytherapy. A recent study tried to assess radiobiological restrictions and tolerance doses as well as other toxic effects derived from repeated applications of single-fraction HDR irradiation of small liver volumes.[33] The author reported that inactivation of liver parenchyma occurs at a BED of approximately 22–24 Gy corresponding to a single dose of ~10 Gy (alpha/beta ~5 Gy). This tolerance dose is consistent with the large potential to treat oligotopic and/or recurrent liver metastases by computed tomography (CT)-guided HDR brachytherapy without RILD. In another study, which tried to determine the safety and efficacy of CT-guided brachytherapy in hepatocellular carcinoma,[34] the authors performed 124 CT-guided brachytherapy sessions on 83 patients with one to three lesions per treatment. A high rate of local control was observed, regardless of applied dose in a range of 15–25 Gy. Although they reported nine complications requiring intervention, they found no evidence for RILD. However, there is a lack of studies in the literature, where dose–volume metrics and BED are correlated with RILD after HDR brachytherapy to make a direct comparison of the presented results.

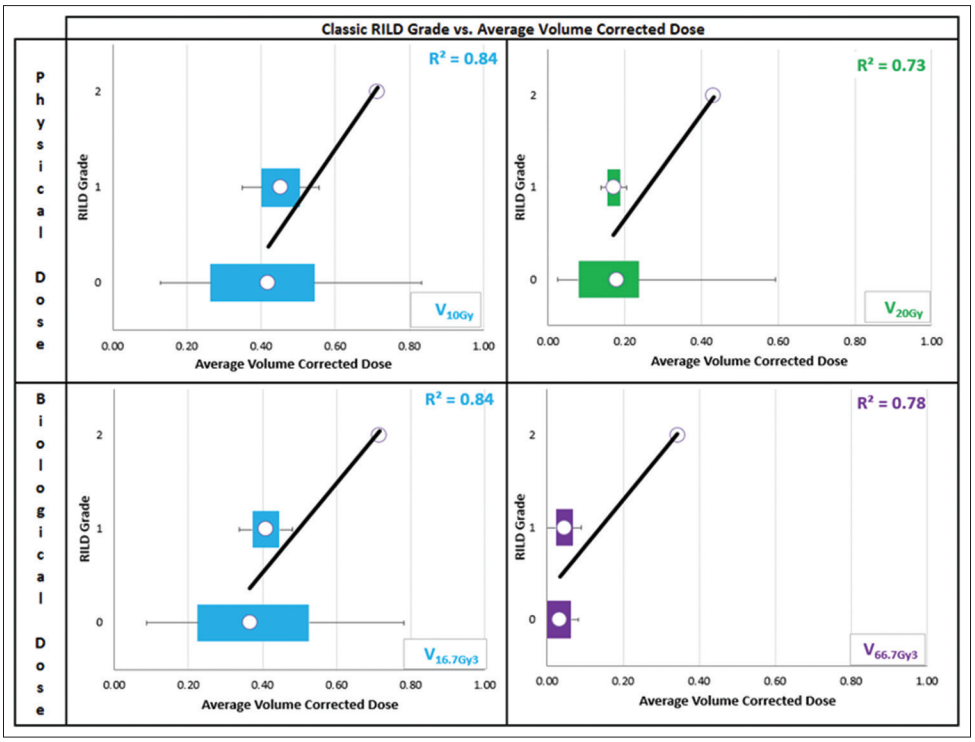

Figure 2: Box-and-whisker plots of the two most closely correlated dose-levels to classic radiation-induced liver disease corresponding to the V_{10Gy} and V_{20Gy} physical doses and the $V_{16.7Gy3}$ and $V_{66.7Gy3}$ biological effective dose values

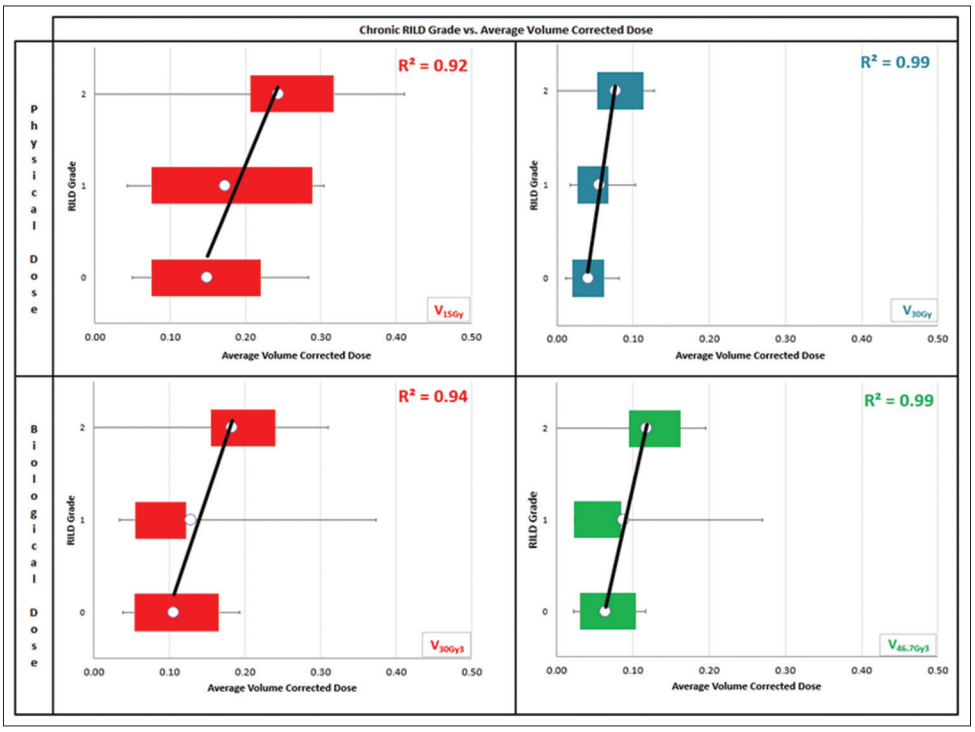

Figure 3: Box-and-whisker plots of the two most closely correlated dose-levels to chronic radiation-induced liver disease corresponding to the V_{15Gy} and V_{30Gy} physical doses however, with the biological effective dose–volumes of V_{30Gy3} and $V_{46.7Gy3}$

In this study, the authors convert the different PDs to a common fractionation scheme to correlate them with RILD. However, this process is relying on the accuracy of the LQ and LQ-L models as well as on the accuracy by which the α/β value was determined. Even though the knowledge of those two factors is at a good level, the use of a higher number of patients where the different groups would equally be represented would give a more clear and reliable picture of the examined correlations.

Conclusion

This institutional retrospective review of hypofractionated treatments led to two main findings. The first is that the dose–volume metrics V_{10Gy} and V_{15Gy} are closely correlated with both classic and chronic RILD, which confirms the appropriateness of using the PD of 15 Gy as a constraint. A further investigation of these dose levels for RILD may yield their increased predictive power regarding immediate and lasting complications. The second finding is that the close correlation of BED with both RILD categories indicates its potential to be used as a treatment evaluator irrespective of the fractionation scheme applied. This study reaffirms that lower dose–volume metrics may prove prudent in biological relation in both immediate and lasting liver toxicities for hypofractionation and SBRT.

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Conflicts of interest

There are no conflicts of interest.

References

1. Tse RV, Hawkins M, Lockwood G, Kim JJ, Cummings B, Knox J, *et al.* Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol 2008;26:657-64.
2. Lock MI, Hoyer M, Bydder SA, Okunieff P, Hahn CA, Vichare A, *et al.* An international survey on liver metastases radiotherapy. Acta Oncol 2012;51:568-74.
3. Rusthoven KE, Kavanagh BD, Cardenes H, Stieber VW, Burri SH, Feigenberg SJ, *et al.* Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. J Clin Oncol 2009;27:1572-8.
4. Katz AW, Carey-Sampson M, Muhs AG, Milano MT, Schell MC, Okunieff P, *et al.* Hypofractionated stereotactic body radiation therapy (SBRT) for limited hepatic metastases. Int J Radiat Oncol Biol Phys 2007;67:793-8.
5. Lawrence TS, Robertson JM, Anscher MS, Jirtle RL, Ensminger WD, Fajardo LF, *et al.* Hepatic toxicity resulting from cancer treatment. Int J Radiat Oncol Biol Phys 1995;31:1237-48.
6. 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.
7. 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.
8. Common Terminology Criteria for Adverse Events: (CTCAE). Version 4.0. Bethesda, Md.: U.S. Department of Health and Human Services; 2009, 2010.
9. Lee MT, Kim JJ, Dinniwell R, Brierley J, Lockwood G, Wong R, *et al.* Phase I study of individualized stereotactic body radiotherapy of liver metastases. J Clin Oncol 2009;27:1585-91.
10. Kim J, Jung Y. Radiation-induced liver disease: Current understanding and future perspectives. Exp Mol Med 2017;49:e359.
11. Withers HR. Biologic basis for altered fractionation schemes. Cancer 1985;55:2086-95.
12. Hall E. Cell survival curves. Radiobiology for the Radiologist. 5th ed.. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 35-7.
13. Elkind MM, Sutton H. X-ray damage and recovery in mammalian cells in culture. Nature 1959;184:1293-5.
14. Barendsen GW. Dose fractionation, dose rate and ISO-effect relationships for normal tissue responses. Int J Radiat Oncol Biol Phys 1982;8:1981-97.
15. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol 1989;62:679-94.
16. Jones B, Tan LT, Dale RG. Derivation of the optimum dose per fraction from the linear quadratic model. Br J Radiol 1995;68:894-902.
17. Thames HD, Bentzen SM, Turesson I, Overgaard M, Van den Bogaert W. Time-dose factors in radiotherapy: A review of the human data. Radiother Oncol 1990;19:219-35.
18. Fowler JF, Tomé WA, Fenwick JD, Mehta MP. A challenge to traditional radiation oncology. Int J Radiat Oncol Biol Phys 2004;60:1241-56.
19. Puck TT, Marcus PI. Action of x-rays on mammalian cells. J Exp Med 1956;103:653-66.
20. Garcia LM, Wilkins DE, Raaphorst GP. Alpha/beta ratio: A dose range dependence study. Int J Radiat Oncol Biol Phys 2007;67:587-93.
21. Guerrero M, Li XA. Extending the linear-quadratic model for large fraction doses pertinent to stereotactic radiotherapy. Phys Med Biol 2004;49:4825-35.
22. Wang JZ, Mayr NA, Yu WT. A generalized linear-quadratic formula for high-dose-rate brachytherapy and radiosurgery. Int J Radiat Oncol Biol Phys 2007;69:S619-20.
23. Park C. The unifying hybrid survival curve and single fraction equivalent dose: Useful tools in understanding the potency of ablative radiation therapy. Int J Radiat Oncol Biol Phys 2008;70:847-52.
24. Astrahan M. Some implications of linear-quadratic-linear radiation dose-response with regard to hypofractionation. Med Phys 2008;35:4161-72.
25. Dawson LA, Normolle D, Balter JM, McGinn CJ, Lawrence TS, Ten Haken RK, *et al.* Analysis of radiation-induced liver disease using the lyman NTCP model. Int J Radiat Oncol Biol Phys 2002;53:810-21.
26. Atwood KC, Norman A. On the interpretation of multi-hit survival curves. Proc Natl Acad Sci U S A 1949;35:696-709.
27. Carlone M, Wilkins D, Raaphorst P. The modified linear-quadratic model of Guerrero and Li can be derived from a mechanistic basis and exhibits linear-quadratic-linear behaviour. Phys Med Biol 2005;50:L9-13.
28. Radiation Therapy Oncology Group. Study Protocol 0438. A Phase I Trial of Highly Conformal Radiation Therapy for Patients with Liver Metastases. Radiation Therapy Oncology Group; 2013.
29. Hall E. Time, dose, and fractionation in radiotherapy. Radiobiology for the Radiologist. 5th ed.. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 327.
30. Wharton JT, Delclos L, Gallager S, Smith JP. Radiation hepatitis induced by abdominal irradiation with the cobalt 60 moving strip technique. Am J Roentgenol Radium Ther Nucl Med 1973;117:73-80.
31. Pan CC, Kavanagh BD, Dawson LA. Quantitative analysis of normal tissue effects in the clinic: Radiation-associated liver injury. Int J Radiat Oncol Biol Phys 2010;76:94-100.
32. Kavanagh BD, Schefter TE, Cardenes HR, Stieber VW, Raben D, Timmerman RD, *et al.* Interim analysis of a prospective phase I/II trial of SBRT for liver metastases. Acta Oncol 2006;45:848-55.
33. Rühl R, Lüdemann L, Czarnecka A, Streitparth F, Seidensticker M, Mohnike K, *et al.* Radiobiological restrictions and tolerance doses of repeated single-fraction HDR-irradiation of intersecting small liver volumes for recurrent hepatic metastases. Radiat Oncol 2010;5:44.
34. Mohnike K, Wieners G, Schwartz F, Seidensticker M, Pech M, Ruehl R, *et al.* Computed tomography-guided high-dose-rate brachytherapy in hepatocellular carcinoma: Safety, efficacy, and effect on survival. Int J Radiat Oncol Biol Phys 2010;78:172-9.