Test the Effectiveness of Quantitative Linear-Quadratic-Based (qLQB) Model on Evaluating Irradiation-Induced Liver Injury (ILI) Against Normal Tissue Complication Probability (NTCP)

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Abstract

Objectives: To test the effectiveness of quantitative linear-quadratic-based (qLQB) model on evaluating irradiation-induced liver injury (ILI) and establish the relation between the damaged ratio/percent (DRP) in qLQB model and normal tissue complication probility (NTCP).

Materials and Methods: We established the qLQB model to calculate the ratio/percent (RP) between damaged cell/functional subunit (FSU) and entire cell/FSU of liver for radiation dose response, tested the qLQB against the Lyman-Kutcher-Burman (LKB) model, and established relation between the RP and NTCP through analyzing the dose of 32 patients with cancer of abdominal cavity who were treated with radiation therapy at our department. Based on varied α/β and varied parameters for NTCP, we put the calculated results into varied arrays for the next analysis. We named the 2 groups of RPs: RP1 ($\alpha/\beta = 3.0$, $\alpha = 0.03$) and RP2 ($\alpha/\beta = 8.0$, $\alpha = 0.26$), and named the 2 groups of NTCPs: NTCP1 ($n = 0.32$, $m = 0.15$, TD50(1) = 4000 cGy) and NTCP2 ($n = 1.10$, $m = 0.28$, TD50(1) = 4050 cGy).

Results: Spearman correlation analysis was used to analyze the correlations among the groups, the results were as follows: RP1 vs NTCP1, rs = 0.83827, p < 0.0001; RP1 vs NTCP2, rs = 0.83827, p < 0.0001; RP2 vs NTCP2, rs = 0.79289, p < 0.0001; and RP2 vs NTCP1, rs = 0.79289, p < 0.0001.

Conclusions: There is a significant correlation between RP value and NTCP for evaluating ILI, and there is no difference between qLQB model and LKB model on evaluating ILI.

Introduction

The liver is an important organ that needs to be protected during radiotherapy for tumors in the lower abdomen.[1,2] The liver is relatively slow to renew, and the average lifetime of liver cells is about 1 year. However, under the strong stimulation of partial liver resection or fatal injury, all liver cells will quickly enter the period of proliferation. Radiation to an abdominal tumor is bound to damage the liver, and slight damage can lead to some dysfunction, but not any functional consequences.[3,4] When the liver is exposed to a relatively high dose of radiation or has serious damage occurrence, the liver tolerates well in the first few months, but then the liver develops progressive degeneration, due to the normal functional activity of irradiated liver cells but the inability to divide.

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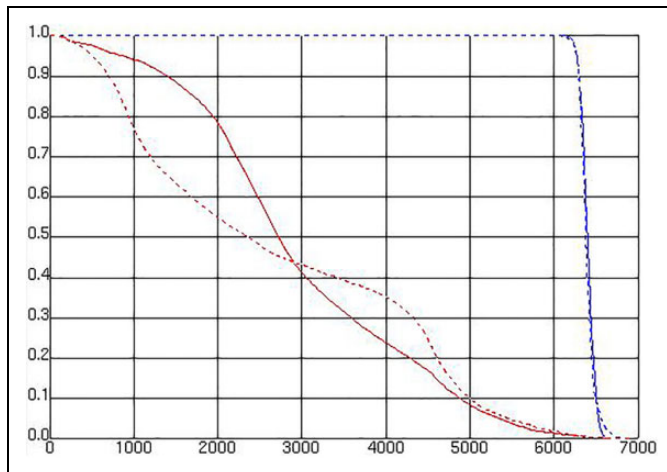Email: 916133705@qq.com

Figure 1. DVH display of 2 plans.

In the clinical practice, Vx or $Dx\%$ (Vx is the percentage between the volume receiving the dose equal to and greater than x and the total organ volume. The Vx and $Dx\%$ can be converted into each other, and for example, the information expressed by $D_{50\%} = 30.0$ Gy and $V_{30} = 50.0\%$ is the same.) is usually used to evaluate the radiotherapy physical plan (RPP) and predict the degree of irradiation-induced liver injury (ILI). However, when using Vx to evaluate and optimally select RPP, 2 problems are often encountered. One is that there are many Vx related to ILI. Liang et al. showed that mean dose to normal liver (MDTNL) >23.0 Gy and $V_5 > 86.0\%$, $V_{10} > 68.0\%$, $V_{15} > 59.0\%$, $V_{20} > 49.0\%$, $V_{25} > 35.0\%$, $V_{30} > 28.0\%$, $V_{35} > 25.0\%$ and $V_{40} > 20.0\%$ were all risk factors for ILI.[5] Dawson et al. found that mean liver dose > 31.0 Gy was the risk factor for ILI. If the probability of occurrence of ILI was 5.0%, 1/3 of the liver receiving the dose of > 90.0 Gy and 2/3 of the liver receiving the dose of > 47.0 Gy were also the risk factors for ILI.[6] It can be seen that ILI is a complex problem. And the other is that using different Vx to select RPP will get different results. For example, the imaginary and full lines in Figure 1 represented Plan1 and Plan2 designed for the same liver tumor patient, respectively. When using V_{20} to optimally select RPP, the Plan1 will be selected, and when using V_{40} to optimally select RPP, the Plan2 will be selected.

In order to overcome the difficulties encountered by using Vx to evaluating plan, our research team based on irradiation-induced lung injury established linear-quadratic-based (LQB) model and quantitative LQB (qLQB) model, and verified the effectiveness of the 2 models on evaluating irradiation-induced lung injury. In this study, we tested the effectiveness of qLQB model on evaluating ILI against LKB model, and then established the relation between the RP in qLQB model and NTCP of ILI for the qLQB model to be applied to all parallel organs in the body.

Materials and Methods

Patients' Base Data

A total of 32 postoperative patients with cancer of abdominal cavity who were treated with radiation therapy at our department from June 2015 to February 2016 were enrolled in this study. Each patient underwent Siemens computed tomography scan with 120 kV and 80 mA and reconstructed with 2.5mm-layer, and was transferred to treatment planning system (TPS). Among 32 patients, 8 patients had gastric carcinoma, 18 patients had liver carcinoma, and 6 patients had pancreatic carcinoma. The plan data set consisted of 32 IMRT plans with 5-7 fields based on Pinnacle TPS 9.6 and Varian IX with 80 pairs of multi-leaf collimator. Dose calculation grid size was set 2.5 mm for every plan.

The targets, which included high-risk clinical tumor volume (CTV1) and low-risk clinical tumor volume (CTV2) and OARs for areas that included the normal liver, spinal cord, small intestine, kidney, et al. were delineated. CTV1 and CTV2 were expanded with 5.0 to 8.0 mm margin and for high-risk planning tumor volume (PTV1) and low-risk planning tumor volume (PTV2), respectively. The institutional planning criteria for cancer treatment were applied according to RTOG0615, and the prescription dose should cover at least 95% of the PTV. The recommended dose, 50Gy/25F and 45Gy/25F, 50Gy/25F and 60Gy/25F, 50Gy/25F and 56Gy/25F acted as prescription for GC's PTV1 and PTV2, LC's PTV1 and PTV2, PC's PTV1 and PTV2, respectively. A significant dose gradient was observed between the target and normal tissues in all cancers. The dosimetric constraints recommended for the organs were according to RTOG0615 and RTOG0225.

qLQB Model

The qLQB model was established and applied based on the following 3 assumptions:

a) The parallel organs in human body, such as lung, liver and kidney, et al. were ideal parallel organs, that is, all function subunits (FSUs) were parallel and independent, and FSU was evenly distributed in the volume of the whole organ. Under the condition of a certain number of cells losing proliferation capacity, normal tissues will have acute and chronic radiation effect.

b) In all dose ranges, the survival fraction (SF) and dose (D) of the cells always met the formula $SF = e^{-\alpha D - \beta D^2}$.

c) The relationship between survival of cells and the survival of FSU was rectilinear correlation.

The liver is a parallel organ, and the probability of radiation complications is closely related to the volume ratio of damage. Liver is assumed to be an organ of uniform density, volume ratio is the percentage of cell damage. Based on the above 3 assumptions, we have established the qLQB model to calculate the ratio/percent (RP) between damaged cell/FSU and entire cell/FSU of liver for radiation dose response, test the qLQB against the Lyman-Kutcher-Burman (LKB) model and establish relation between the RP and NTCP. The qLQB model can be described by a formulae[7]:

$$RP = \frac{A \times V - \sum_{D=0}^{D=D_{\max}} A \times (e^{-\frac{\alpha D}{f_1(D) \times V_s} - \frac{\beta D^2}{f_1^2(D) \times V_s^2}})^n \times f_1(D) \times V_s}{A \times V_s}$$

(1)

Here, A is the number of cells in a unit; Vs is the integral volume of normal liver; Dmax is the maximum dose which is exposed on normal liver per fraction in the plan. f_1(D) is the percentage volume of liver which is exposed at dose D. V is the integral exposed volume of liver. α and β are dimensionless parameter, which are determined by the organ character. The process of the qLQB establishment and brief descriptions of the LKB model are given **in the Appendix A.**

RP and NTCP Calculation

To calculate the RP value, the author obtains D and it's corresponding f_1(D) from dose-volume statistical table of differential diagram of dose-volume histogram (dDVH). From $D = 0$ to $D = Dmax$, the auther abtains all D value by step of 1 cGy, because by step of <1 cGy the value of RP is almost constant. Exposed volume of liver is determined with the low limit of dose. If the low limit of dose is too low, for example 0.1cGy/F, 0.05cGy/F, et al., the whole liver is involved in every radio therapy even if the tumor is in the choracic cavity. To avoid this state, the author sets the low limit of dose at 1cGy/F, the causes are as follows: 1) If step being <1 cGy the value of RP is almost constant. 2) The injury brought about by <1 cGy which can be repaired before the next treatment.

Liver is often considered an organ, but up to date, it's radiotherapic parameters aren't acknowledged completely. To avoid the study enter into a 1-sided result, in this study the author employed 2 groups of α, β values for calculating RP: $\alpha/\beta = 3.0, \alpha = 0.03$,[8] and $\alpha/\beta = 8.0, \alpha = 0.26$.[9,10] And employed 2 groups of TD50(1), m, n values for calculating NTCP in LKB model: n = 0.32, m = 0.15, TD50(1) = 4000cGy,[11] and n = 1.10, m = 0.28, TD50(1) = 4050cGy.[12]

Results

To conveniently discuss, the author named the 2 groups of RPs (each group of RPs has 32 values corresponding to 32 patients): RP1 ($\alpha/\beta = 3.0, \alpha = 0.03$) and RP2 ($\alpha/\beta = 8.0, \alpha = 0.26$), and named the 2 groups of NTCPs (each group of NTCPs has 32 values corresponding to 32 patients): NTCP1 (n = 0.32, m = 0.15, TD50(1)= 4000 cGy) and NTCP2 (n = 1.10, m = 0.28, TD50(1)= 4050 cGy). Then the Spearman correlation was used to analyze values above 4 groups, the results are as follows: RP1 vs NTCP1, rs = 0.83827, p < 0.0001; RP1 vs NTCP2, rs = 0.83827, p < 0.0001; RP2 vs NTCP2, rs = 0.79289, p < 0.0001; and RP2 vs NTCP1, rs = 0.79289, p < 0.0001. So, there is a positive correlation between qLQB model and LKB model for evaluating ILI, and this correlation are displayed in Figures 2, 3, 4 and 5.
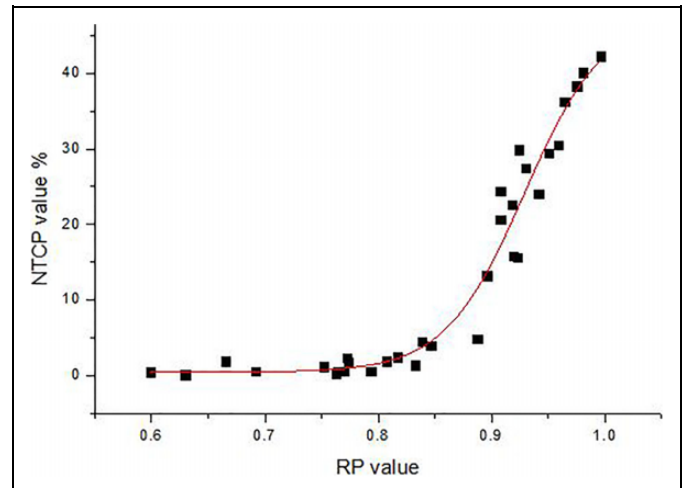

Figure 2. Relationship between RP value and NTCP. When calculated RP value and NTCP, the parameters were selected as follows: α/β = 3.0, α = 0.03; n = 0.32, m = 0.15, TD50(1) = 4000 cGy.
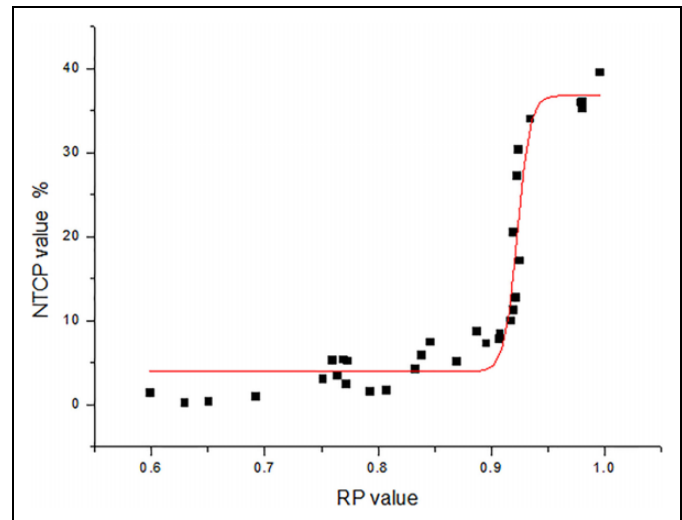

Figure 3. Relationship between RP value and NTCP. When calculated RP value and NTCP, the parameters were selected as follows: α/β = 3.0, α = 0.03; n = 1.10, m = 0.28, TD50(1) = 4050 cGy.

Discussion

The fundamental goal of radiotherapy is to give the tumor a therapeutic dose while minimizing the risk of normal tissue complications. Until now, the commonly used indicator for assessing the risk of liver complication has Vx, which is an agency of radio-biological responses and does not directly reflect liver complication risk. Several studies had reported that partial volume irradiation of the liver is feasible.[13,14] And it is well known that the tolerance of the liver to external beam irradiation depends on the volume of liver irradiated, few data exist which quantify this dependence. Radiation-induced liver disease is one of ILI, a well-established concept, a serious hepatic toxicity caused by irradiation of 30-35 Gy to the whole liver.[15] Although clinical practice indicates that the level of ILI

Figure 4. Relationship between RP value and NTCP. When calculated RP value and NTCP, the parameters were selected as follows: $\alpha/\beta = 8.0$, $\alpha = 0.26$; $n = 0.32$, $m = 0.15$, TD50(1)= 4000 cGy.
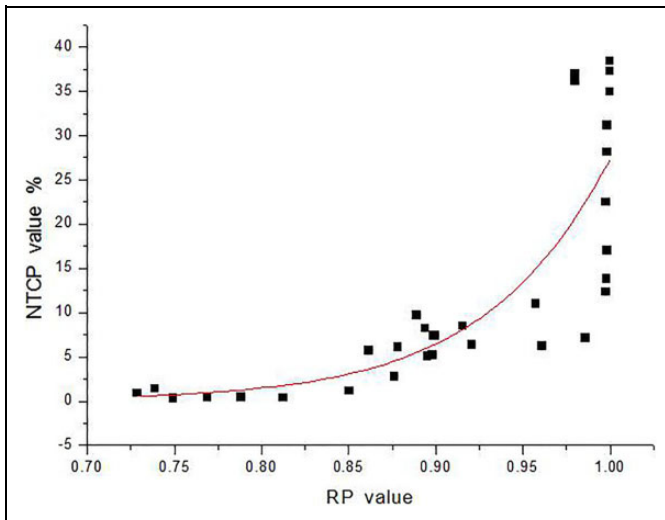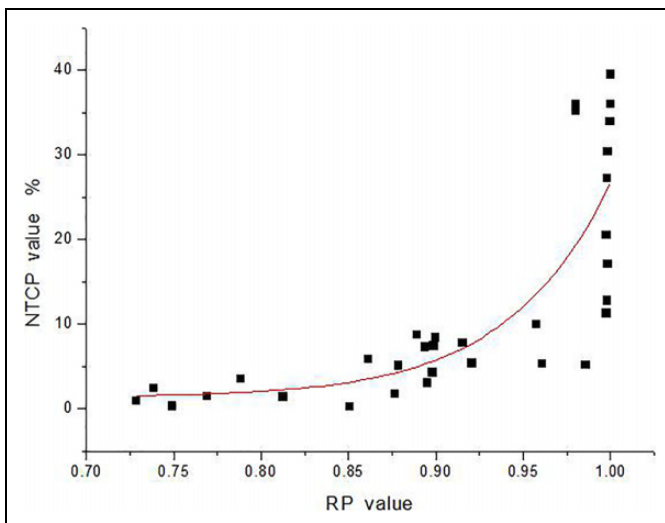

Figure 5. Relationship between RP value and NTCP. When calculated RP value and NTCP, the parameters were selected as follows: $\alpha/\beta = 8.0$, $\alpha = 0.26$; $n = 1.10$, $m = 0.28$, TD50(1)= 4050 cGy.

is related with exposed-volume of liver and dose exposed on the volume, we haven't knowed their specific relation.

The early NTCP model was mainly derived from clinical observation, and generally included 2 factors, overall treatment time and fractionation. In order to calibrate the differences caused by these 2 factors, the formulas such as nominal standard dose (NSD), cumulative radiation effect (CRE) and time, dose and fractionation (TDF) were proposed.[16] Later, with the development of radiobiology and the update of radiotherapy technology, multiple NTCP models were proposed in attempts to quantify dependence of tolerance effect for a certain radiation effect on the size of the treated region.[17,18] Although, up to now, we still haven't found a model, and the calculated results are completely consistent with the clinical results because of

the uncertainty of models' parameters and the complexity of clinical practice. However, it is undeniable that these models provide a good reference for us to evaluate the plan.

LKB model is good and widely used model, which can be used to analyze ILI not considering Vx. We test the effectiveness of the qLQB model against the LKB model, acquiring rs > 0.79 (0.793, 0.837) and p < 0.0001, indicating there is a abvious positive correlation between RP values in qLQB model and NTCP values in LKB model, and use of the LKB model or the LQ-based model will obtain the same results for evaluating level of ILI.

The model established by Lyman can be used to describe dose response only when the absorbed dose is uniform dose. But the precise radiotherapy increases rapidly non-uniform degree of normal organs absorbed dose. Although Kutcher and Burman had improved the model, non-uniform dose must be converted some uniform dose before using the integral model. But qLQB model is based on LQ model, which can be used to describe dose response directly using non-uniform dose. Secondly, LKB model is a experiential model based on 4 parameters, and the base of qLQB model, LQ model, was from a radiation biology experiment, which is more reliable than experiential parameters. Thirdly, qLQB is not only based on in vitro LQ model but also based on in vivo LQ model, which can increase consistency between calculation base on qLQB model, if which is based on in vivo LQ model, and clinical outcomes in the future. Fourthly, the LKB model only contains information on the total dose, without the total treatment time and fractionation, which are important factors for biological effects. The qLQB model can reflect fractionation and other information through the LQ model, because we can convert a physical radiotherapy planning to a biological radiotherapy planning.[19] Fifthly, LQ model is widely used in clinical practice,[19-23] indicating that the qLQB model based on LQ model has the potential possibility to be widely used in clinical practice. Finally, the established process of qLQB model provides us a method, by which we can convert the laws (models) obtained from radiobiology into practical models available in clinical practice.

Although an α/β ratio of 3 could be used to calculate for most of the parallel organ which is widely acknowleged,[8] the α/β ratio of normal liver is unknown. Various ranges of α/β ratio were used with respect to various different criteria of ILI in previous studies. To calculate the BED delivered to the normal liver, α/β ratio of 2 was used for grade 3 or worse CTCAE hepatic toxicity.[24] Son et al. used α/β ratio of 2, 4, 6, 8 or 10 for 2 groups, Group A (45-50 Gy, 4.5-5.0 Gy) and Group B (36-60 Gy, 2.5-3.0 Gy), of liver patients. And then suggested that α/β ratio of normal liver is 8.[10] Dawson et al. used an α/β ratio of 2 or 2.5 for cases of classic RILD.[24,25]

Although the qLQB model overcomes limitations of Vx and has some advancement than LKB model, there are several problems requiring more attention and further study regarding the use of qLQB model in the clinic setting. The qLQB model is based on the LQ model, but the LQ model is obtained in vitro. So, actual RP in vivo should be more lower than

calculated RP based on qLQB model in this paper, because of proliferation in vivo.

Appendix

Appendix A: The Establishment of qLQB Medol and LKB Model

The Establishment of qLQB Medol[7]

For radiobiology and radiotherapy, the function which can be described as a connection between exposed dose and cell survival fraction is very significant. In 1956, Puck established the first cell survival experimental curves of mammal cells when he studied the quantitative relation of irradiation dose and cell survival fraction. The curve shape could be described by the presence of an initial slope at low doses, followed by a shoulder and a final slope at the high dose end of the survival curve. Subsequent experiments display the shape of cell survival curves is varied because of cell lines, dose rate, etc.

Studies of the shape of cell survival curves and general mathematical models have important objectives. Radiation oncology investigators have established some mathematical models to fit experimental data including the index deactivation mathematical model, SF = e-αD; single-hit multi-target model, SF = 1-(1-e-kD)N; and LQ model, SF = e-αD-βD^2. However, universal theory on cell deactivation after irradiation in vivo has been not realized up to now.

The LQ model is one of general applied representative mathematical models for cell survival analysis. It is hypothesized that deactivated cells consist of 2 parts, 1 part is proportional to irradiation dose –αD, and the other is proportional to the square of irradiation dose -βD^2.

$$SF = e - \alpha D - \beta D^2 \qquad ([A.1])$$

Here, SF is cell survival fraction of cells which are exposed with dose D, and α and β are constants related with ray character and cell kind. Based on the model, we can obtain a continuous curved cell survival curve, and the relationship between D and SF is degressive and one-to-one.

Aiming at utilization conveniences, in this paper we define the LQ model into unit volume(cm3), given by

$$sf = e - \alpha d - \beta d^2 \qquad ([A.2])$$

Here, sf is the cell survival fraction of cells in a unit volume (cm3) exposed with dose d. Then cell survival fraction of cells in a unit volume, sf(n), after n fractions with a dose of d per fraction, is given by

$$sf(n) = (e - \alpha d - \beta d^2)n \qquad ([A.3])$$

When evaluating plan or selecting the best plan, radiotherapists usually evaluate and compare the Dose-Volume-Histogram (DVH), while ignoring the dose-Volume-Differential-Histogram (dDVH), which results in us losing some information that may be important.

With dDVH in a designed plan, we can acknowledge exactly the percentage volume f1(D) of lung which is exposed at dose D. Assuming the integral volume of lung is Vs, the volume which is exposed at dose D is VD,

$$VD, = f1(D) \times Vs \qquad ([A.4])$$

Then

$$d = D / V_D, \qquad ([A.5])$$

If we substitute d into [A.3], we can acquire sf(n) in a unit volume (cm3) after n fractions with a dose of d Gy per fraction. Assuming the number of cells in a unit volume (cm3) is A, and the number of survival cell in a unit volume (cm3) is a, then the a is given by

$$a = A \times sf(n) \qquad ([A.6])$$

In the volume of lung which is exposed at dose D, the total number of survival cell b is:

$$b = a \times V_D, \qquad ([A.7])$$

Joining [A.3] [A.4] [A.5] [A.6] [A.7], a available formula is given by:

$$b = A \times (e^{-\frac{\alpha D}{f_1(D) \times V_s} - \frac{\beta D^2}{f_1^2(D) \times V_s^2}})^n \times f_1(D) \times V_s \qquad ([A.8])$$

Then, by summing all the b values, we will obtain the sum of the number of survival cells in lung (except the part in lung which is not exposed to ray) after irradiation.

$$b_{sum} = \sum_{D=0}^{D=D_{max}} A \times (e^{-\frac{\alpha D}{f_1(D) \times V_s} - \frac{\beta D^2}{f_1^2(D) \times V_s^2}})^n \times f_1(D) \times V_s \qquad ([A.9])$$

Here, Dmax is the maximum dose which is exposed on lung per fraction in the plan.

By formula [A.9], radiotherapists can acquire bsum for selecting the best plan, in terms of lung, among several plans for the same patient, which is adequately demonstrated in our other paper.

Assuming the integral exposed volume of lung is V, we can acquire a formula, through which we can easily acquire the ratio/percent(R/P) between damaged cell and entire cell of lung.The formula is given by:

$$RP = \frac{A \times V - \sum_{D=0}^{D=D_{max}} A \times (e^{-\frac{\alpha D}{f_1(D) \times V_s} - \frac{\beta D^2}{f_1^2(D) \times V_s^2}})^n \times f_1(D) \times V_s}{A \times V_s}$$
$$([A.10])$$

LKB Model[11]

In the Lyman-Kutcher-Burman model, NTCP for uniform irradiation of an organ with the dose D is given by

$$NTCP = 1/\sqrt{2\pi} \int_{-\infty}^{u} e^{-t^2/2} dt \qquad ([A.11])$$

Where

$$u = (D - TD50(v))/(mTD50(v)) \qquad ([A.12])$$

m is a dimensionless parameter and TD50 is the whole organ dose for which NTCP is 50%.

For the case of uniform irradiation of a fractional volume v to dose D, Lyman gives the NTCP by the same formula with TD50 replaced by a partial-volume-dependent parameter TD50(v), given by

$$TD50(v) = TD50(1) \times v^{-n} \qquad ([A.13])$$

The exponent, with n > 0, is the parameter that determines volume dependence and TD50(1) = TD50(v), the value for uniform organ irradiation. For the sake of brevity in the following, when the meaning is clear from the context, we shall simple abbreviate TD50(1) as TD50(v). The fractional volume v is written as v = V/Vref where Vref is a referenced volume for the OAR, usually taken to refer to the entire volume of the OAR.

Author Contribution

Bai and Wang are authors contributed equally to this study and share first authorship.

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References

1. Jung J, Yoon SM, Kim SY, et al. Radiation-induced liver disease after stereotactic body radiotherapy for small hepatocellular carcinoma: clinical and dose-volumetric parameters. *Radiat Oncol*. 2013;27(8):249-255.

2. Zhao Q, Wang R, Zhu J, et al. Superiority of helical tomotherapy on liver sparing and dose escalation in hepatocellular carcinoma: a comparison study of three-dimensional conformal radiotherapy and intensity-modulated radiotherapy. *Onco Targets Ther*. 2016;9(5):3807-3813.

3. Feng M, Suresh K, Schipper MJ, Lawrence TS, 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):40-47.

4. Fukugawa Y, Namimoto T, Toya R, et al. Radiation-induced Liver Injury after 3D-conformal Radiotherapy for hepatocellular carcinoma: quantitative assessment using Gd-EOB-DTPA-enhanced MRI. *Acta Med Okayama*. 2017;71(1):25-29.

5. Liang SX, Zhu XD, Xu ZY, 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(2):426-434.

6. Dawson LA, Ten Haken RK, Lawrence TS. Partial irradiation of the liver. *Semin Radiat Oncol*. 2001;11(3):240-246.

7. Wang L, Li W, Bai H, Cui J, Qin J, Chang L. A quantitative LQ-based model for lung injury in radiotherapy. *Technol Cancer Res Treat*. 2015;14(5):531-538.

8. Dubray B, Henry-Amar M, Meerwaldt JH, et al. Radiation-induced lung damage after thoracic irradiation for Hodgkin's disease: the role of fractionation. *Radiother Oncol*. 1995;36(3):211-217.

9. Rutkowska E, Baker C, Nahum A. Mechanistic simulation of normal-tissue damage in radiotherapy—implications for dose-volume analyses. *Phys Med Biol*. 2010;55(8):2121-2136.

10. Son SH, Jang HS, Lee H, et al. Determination of the α/β ratio for the normal liver on the basis of radiation-induced hepatic toxicities in patients with hepatocellular carcinoma. *Radiat Oncol*. 2013;15(8):61-75.

11. Luxton G, Keall PJ, King CR. A new formula for normal tissue complication probability (NTCP) as a function of equivalent uniform dose (EUD). *Phys Med Biol*. 2008;53(1):23-36.

12. Liang SX, Huang XB, Zhu XD, et al. Dosimetric predictor identification for radiation-induced liver disease after hypofractionated conformal radiotherapy for primary liver carcinoma patients with Child-Pugh Grade A cirrhosis. *Radiother Oncol*, 2011;98(2):265-269.

13. Liu Y, Shi C, Cui M, Wang Y, Yang Z, Gan D. Different doses of partial liver irradiation promotes hepatic regeneration in rat. *Int J Clin Exp Pathol*. 2015;8(6):6554-6559.

14. Aitken KL, Tait DM, Nutting CM, Hawkins MA, Khabra K. Risk-adapted strategy partial liver irradiation for the treatment of large volume metastatic liver disease. *Acta Oncol*. 2014;53(5):702-706.

15. Chang DT, Swaminath A, Kozak M, Weintraub J, et al. Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis. *Cancer*. 2011;117(17):4060-4069.

16. Orton CG, Ellis F. A simplification in the use of the NSD concept in practical radiotherapy. *Br J Radiol*. 1973;46(547):529-537.

17. Thieke C, Bortfeld T, Niemierko A, Nill S. From physical dose constraints to equivalent uniform dose constraints in inverse radiotherapy planning. *Med Phys*. 2003;30(9):2332-2339.

18. Wu Q, Djajaputra D, Wu Y, Mohan R, Zhou J, Liu HH. Intensity-modulated radiotherapy optimization with gEUD-guided dose-volume objectives. *Phys Med Biol*. 2003;48(3):279-291.

19. Koukourakis MI, Damilakis J. LQ-based model for biological radiotherapy planning. *Med Dosim*. 1994;19(4):269-277.

20. Franken NA, Oei AL, Kok HP, et al. Cell survival and radiosensitisation: modulation of the linear and quadratic parameters of the LQ model (review). *Int J Oncol*. 2013;42(5):1501-1515.

21. Bruni C, Conte F, Papa F, Sinisgalli C. Optimal number and sizes of the doses in fractionated radiotherapy according to the LQ model. *Math Med Biol*. 2019;36(1):1-53.

22. Kim M, Phillips MH. A feasibility study of spatiotemporally integrated radiotherapy using the LQ model. *Phys Med Biol*. 2018; 63(24):245016.

23. Jones B, Hopewell JW. Spinal cord re-treatments using photon and proton based radiotherapy: LQ-derived tolerance doses. *Phys Med*. 2019;64(8):304-310.

24. 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(4):810-821.

25. Dawson LA, Biersack M, Lockwood G, Eisbruch A, Lawrence TS, Ten Haken RK. Use of principal component analysis to evaluate the partial organ tolerance of normal tissues to radiation. *Int J Radiat Oncol Biol Phys*. 2005;62(3): 829-837.