Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 3, pp. 900–907, 2008

0360-3016/08/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2007.10.037

PHYSICS CONTRIBUTION

ESTIMATE OF RADIOBIOLOGIC PARAMETERS FROM CLINICAL DATA FOR BIOLOGICALLY BASED TREATMENT PLANNING FOR LIVER IRRADIATION

AN TAI, PH.D., BETH ERICKSON, M.D., KEVIN A. KHATER, PH.D, M.D., AND X. ALLEN LI, PH.D.

Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI

Purpose: The Radiation Therapy Oncology Group (RTOG) is initiating a few new hypofractionation regimens (RTOG 0438) to treat liver cancer patients. To evaluate the radiobiologic equivalence between different regimens requires reliable radiobiologic parameters. The purpose of this work is to estimate a plausible set of such parameters for liver tumors and to design new optimized dose fractionation schemes to increase patient survival.
Methods and Materials: A model was developed to fit clinical survival data from irradiation of a series of primary liver patients. The model consists of six parameters including radiosensitivity parameters α and α/β, potential doubling time T_d. Using this model together with the Lyman model for calculations of the normal tissue complication probability, we designed a series of hypofractionated treatment strategies for liver irradiation.
Results: The radiobiologic parameters for liver tumors were estimated to be: $\alpha/\beta = 15.0 \pm 2.0$ Gy, $\alpha = 0.010 \pm 0.001$ Gy^{-1}, $T_d = 128 \pm 12$ day. By calculating the biologically effective dose using the obtained parameters, it is found that for liver patients with an effective liver volume of ~45% the dose fractionation regimens suggested in RTOG 0438 can be escalated to higher dose for improved patient survival (~80% at 1 year) while keeping the normal tissue complication probability to less than 10%.
Conclusions: A plausible set of radiobiologic parameters has been obtained based on clinical data. These parameters may be used for radiation treatment planning of liver tumors, in particular, for the design of new treatment regimens aimed at dose escalation.

Radiobiologic parameter, Survival rate, Lyman model, Hypofractionation.

INTRODUCTION

The incidence of hepatic malignancies is growing (1). Complete resection has been recognized as the most effective therapy for liver tumors. Unfortunately a significant portion of patients with primary liver tumors are not suitable for surgery at diagnosis because of either technical or medical considerations (2, 3). As a result, there is increasing interest in the treatment of hepatic malignancies with radiation therapy. Most hepatic malignancies are not sensitive to radiation, and efforts to escalate the dose are hampered by limited data on radiation-induced liver disease. On the other hand, successful outcomes using proton beams indicates that a tumoricidal dose can be achieved so long as normal liver sparing is under control (4).

Encouraging survival results of a Phase II trial for treating unresectable intrahepatic malignancies by three-dimensional conformal radiation therapy at 1.5 Gy per fraction and 10 fractions per week justify the importance of individualized prospective treatment planning through a calculation of the normal tissue complication probability (NTCP) by the Lyman model (5). Meanwhile the trial also demonstrates that the total dose is a significant prognostic factor for the patient survival, a conclusion also supported by other clinical data (6, 7). From a radiobiologic point of view, the clinical outcome is also related to how the prescribed dose is delivered, that is, the dose fractionation scheme. An optimized treatment strategy should also take into account the dose per fraction and the treatment time in addition to the total dose.

Various dose fractionation regimens have been applied clinically to treat liver tumors, and patient survival rates have been reported (6–17). A review of the current status of liver tumor irradiation can be found in an article by Hawkins *et al.* (9). A new Radiation Therapy Oncology Group (RTOG) protocol for treating liver metastases with hypofractionation has also been initiated (18). Thus there is a need to compare different dose fractionation schemes and to design new regimens with the goal of enhancing clinical outcomes. One could rely on an NTCP model with parameters determined by clinical data to assist in this regard.

Reprint requests to: X. Allen Li, Ph.D., Department of Radiation Oncology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226. Tel: (414) 805-4362; Fax: (414) 805-4354; E-mail: ali@mcw.edu

This work was presented at the 48th Annual Meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO), November 5–9, 2006, Philadelphia, PA.

Conflict of interest: none.

Acknowledgments—The authors thank Drs. X. Sharon Qi and V. Semenenko for helpful discussions. This work was supported in part by the MCW Cancer Center Meinerz Foundation.

Received May 17, 2007, and in revised form Oct 23, 2007. Accepted for publication Oct 24, 2007.

An optimized treatment plan needs to minimize NTCP and to maximize patient survival simultaneously. The NTCP can be calculated using the Lyman model. The parameters from the Lyman model were extracted at 1.5-Gy fraction by Dawson *et al.* (19). Recently new Lyman model parameters were obtained from a hypofractionated regimen of 4.6 Gy (range, 4–6 Gy) (20). However little is known about the radiobiologic parameters for liver tumors. These parameters would help us estimate the tumor control probability, which is closely related to patient survival. We aim to develop a model to extract these parameters directly from published clinical data and to apply them to treatment planning for liver patients.

METHODS AND MATERIALS

Clinical survival rate data

Clinical data used to extract radiobiologic parameters for liver tumors are from three retrospective reviews (6, 8–10). These studies were selected because: (*1*) they have relatively large patient samples ($n > 20$), which reduces the statistical errors of extracted model parameters; (*2*) primary liver tumors were studied, which avoids the problem of tumor metastasis from different primary sites impacting patient survival; (*3*) tumor sizes were comparable, with a median tumor size of ~8 to 10 cm; the median tumor size corresponds to the mean of three orthogonal tumor diameters, and the tumor volume can be approximately calculated by the cubic of the median tumor size; (*4*) survival rates were calculated based on the Kaplan-Meier model and recorded from the first day of radiation treatment; (*5*) different dose fraction schemes were used, enabling one to extract an important radiobiologic parameter α/β (*6*). The NTCP for normal liver were reported and the Lyman model parameters were derived from two of these three institutions (19, 20), enabling a combined study of patient survival and NTCP. These data are summarized in Table 1. The same treatment time was used for three dose bins of data in Seong *et al.* (6), which was calculated by the mean dose of 48.2 Gy and fractional dose 1.8 Gy assuming five fractions per week, *i.e.,* treatment time = 48.2/1.8*7/5 = 37 days.

Primary liver tumors include hepatocellular carcinoma (HCC) and cholangiocarcinoma. Data from Dawson *et al.* (8), Hawkins *et al.* (9), Liang *et al.* (10) were for patients with either HCC or cholangiocarcinoma. Data in Seong *et al.* (6) were for HCC patients only. Tumor stages for patients in Liang *et al.* (10) were 65% (T3) and 35% (T4), and these numbers were 42% (T3) and 58% (T4) for patients in Seong *et al.* (6). Tumor stage was not reported in Dawson *et al.* (8) and Hawkins *et al.* (9), but eligible patients there had to have an estimated life expectancy of at least 12 weeks and Eastern Cooperative Oncology Group performance status of 2 or less. Data from Dawson *et al.* (8) and Hawkins *et al.* (9) include only those patients with liver Child-Pugh A cirrhosis, whereas data in Seong *et al.* (6) and Liang *et al.* (10) include a fraction of Child-Pugh B patients (16% for Liang *et al.* and 26% for Seong *et al.*). In addition patients in Dawson *et al.* (8) and Hawkins *et al.* (9) received concurrent treatments of hepatic arterial chemotherapy, whereas all patients in Seong *et al.* (6) and a fraction of patients (37%) in Liang *et al.* (10) were treated with transcatheter anterial chemoembolization (TACE) before RT.

There were also other clinical data available, but they were not used in this study for various reasons. Survival data in three other series (7, 11, 12, 14) were not recorded from the beginning of radiation treatment, although they were from large patient populations. Time dependence of the survival rates is different when recorded from either diagnosis or radiotherapy (6). The data from two series (13, 17) were not used because the median tumor size of these patients was too small compared with the patients in Table 1. The univariate analysis shows that tumor size is a significant factor of patient survival (6, 7). Data in Herfarth *et al.* (15) were omitted because they were from metastatic liver patients with tumors smaller than 6 cm. Data from Kim *et al.* (16) were for patients in whom transcatheter arterial chemoembolization (TACE) was ineffective or unsuitable, whereas data in Table 1 were from general population of liver patients who were unsuitable for surgery.

Fitting function

We wanted to establish a relationship between the patient survival rate and the dose fractionation scheme for the external beam therapy. For the first trial, we modified a phenomenologic function which was inspired by the linear–quadratic (LQ) formalism (21) and used previously in Qi *et al.* (22) for studying survival rates of brain tumor patients. This function depends on the prescription dose D, the dose per fraction d and elapsed time τ (time between the first radiation treatment and the follow-up) and has the following form

$$SR(D,d,\tau) = e^{-Ke^{-\left[\alpha\left(1+\frac{d}{\alpha/\beta}\right)D-\gamma T-(a(\tau-T))^{\delta}\right]}} \quad \tau>T \qquad (1)$$

where $\gamma = \ln 2/T_d$. α and β characterize the intrinsic radiosensitivity of cells and T_d is the potential doubling time. T is treatment time. K, a and δ are fitting parameters.

The new parameter δ is introduced in order to describe the tumor growth rate for a larger time scale (4–5 years) in contrast to the short follow-up time (1.5 years) of the data in Qi *et al.* (22) and is discussed in further detail in the Results section.

Survival model with cell proliferation

The need of a term $(a(\tau - T))^{\delta}$ in Eq. (1) hints a relationship between the survival rate and tumor clonogens repopulation after radiation therapy. Eq. (1) includes three arbitrary fitting parameters. To provide meanings for model parameters and establish a relationship between repopulation of tumor clonogens and patient survival we develop a simple model based on the following two assumptions: (*1*) a primary liver cancer patient with K tumor cells in the liver will survive if K is smaller than a critical value, i.e. $K<K_{cr}$(otherwise, the patient will die); and (*2*) K_{cr} follow a Gaussian distribution for the

Table 1. Clinical data from three institutions

First author (Ref.)	No. of patients	Median prescribed dose (Gy)	Fraction dose (Gy/fx)	Treatment time (days)	Median survival time (mo)
Liang (10)	128	53.6	4.88	28	20
Dawson (8, 9)	35	61.5	1.5	42	15.2
Seong (6)	83	55	1.8	37	6
Seong (6)	51	45	1.8	37	8
Seong (6)	24	32.5	1.8	37	13

patient population. Then the population averaged patient survival rate can be written as

$$SR(D,d,\tau) = 1 - \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} e^{-\frac{x^2}{2}}dx \ , \qquad (2)$$

where $t = \frac{K-K_{50}}{\sigma_k}$. K_{50} is the critical number of tumor clonogens corresponding to death in 50% patients, and σ_k is the Gaussian width for the distribution of critical clonogen numbers. The dependence of tumor cells on the prescription dose, the dose per fraction, treatment time and elapsed time in this model is described by the following LQ model inspired expression

$$K = K_0 e^{-\left[\alpha\left(1+\frac{d}{\alpha/\beta}\right)D-\gamma T-(\gamma(\tau-T))^{\delta}\right]} \quad \tau>T \qquad (3)$$

where K_0 is the initial number of tumor colonogens. The difference between the similar expression in the LQ model (23), and Eq. (3) is a new term of $(\gamma(\tau - T))^{\delta}$, which characterizes the time dependence of tumor regrowth after completions of radiation therapy.

Combining Eq. (2) and Eq. (3), it is clear that the three parameters, K_0, K_{50} and σ_k, are not independent variables, *i.e.*, they can not uniquely be determined in this model. We then rewrite t as

$$t = \frac{e^{-\left[\alpha\left(1+\frac{d}{\alpha/\beta}\right)D-\gamma T-(\gamma(\tau-T))^{\delta}\right]} - K_{50}/K_0}{\sigma_k/K_0}$$

Goodness of fit

The least Chi-square (χ^2) method is used in our fitting. The free parameters in the fitting functions are determined by minimizing the function, which is defined as

$$\chi^2 = \sum_{i=1}^{n} \frac{\left[SR_i^{theory}(D_i,d_i,\tau_i) - SR_i^{clinic}(D_i,d_i,\tau_i)\right]^2}{\sigma_i^2} \qquad (4)$$

Here $SR_i^{clinic}(D_i,d_i,\tau_i)$and $SR_i^{theory}(D_i,d_i,\tau_i)$ are the survival rate of the i*th* clinically observed data point and the corresponding calculated survival rate, respectively; σ_i is the statistical error of that data point and is calculated by Mathew *et al.* (24):

$$\sigma_i = SR_i^{clinic}\sqrt{\frac{1-SR_i^{clinic}}{N_i}} \qquad (5)$$

where N_i is the number of patients at risk for the i*th* data point. For simplicity, we will take N_i to be the number of survived patients at the time when the i*th* data point is obtained. The goodness of fit is judged by χ^2/dof, where *dof* is the degree of freedom, which is defined to be total number of clinically observed survival data points minus number of free parameters in the fitting function. For an acceptable fit, χ^2/dof should not be significantly greater than 1.0.

Lyman model

For designing an individualized liver treatment plan, aiming at maximizing tumor dose and minimizing dose to normal liver, we apply the Lyman model to calculate the NTCP of radiation induced liver disease. Radiation-induced liver disease is a clinical syndrome of anicteric hepatomegaly, ascites, and elevated liver enzymes occurring 2 weeks to 4 months after completion of radiation treatments. A description of the Lyman model can be found in Dawson *et al.* (19).

The Lyman model has three parameters, $TD_{50}(1)$, *m and n*. TD_{50} (1) is the tolerance dose associated with a 50% NTCP for uniform whole liver irradiation. *m* characterizes the steepness of the dose-response at TD_{50} (1). *n* represents the effect of the irradiated normal liver volume on the tolerance dose associated with a 50% NTCP for uniform partial liver irradiation. A useful quantity in the Lyman model is called the effective volume V_{eff}. It is defined as the normal liver volume, which, if irradiated uniformly to a dose, would be associated with the same NTCP as the nonuniform dose distribution actually delivered with the same dose. V_{eff} is calculated through the normal liver DVH.

The Lyman model parameters for primary liver tumors extracted by Dawson *et al.* at a fractional size of 1.5 Gy (19) are $TD_{50}(1)$ = 39.8 Gy, $m = 0.12$, and $n = 0.97$ (Parameter Set I). These parameters obtained in Xu *et al.* (20) at a fractional size of 4.6 Gy from primary liver patients with Child-Pugh A cirrhosis are $TD_{50}(1)$ = 40.5 Gy, $m = 0.28$, and $n = 1.1$ (Parameter Set II). Different dose per fraction would generate different biologic effects on normal tissue. To calculate NTCP for a given dose fractionation scheme, one has to normalize the dose distribution to the reference dose per fraction at which the Lyman model parameters are extracted. The following expression was suggested (25) to normalize the dose distribution of a dose per fraction d to a reference dose per fraction d_{ref}

$$D_i(d_{ref}) = \left(\frac{\alpha/\beta + d}{\alpha/\beta + d_{ref}}\right)D_i(d) \qquad (6)$$

where $D_i(d)$ is the dose in i*th* bin of the normal liver dose–volume histogram and α/β = 2 Gy for normal tissue. Unfortunately, Eq. (6) leads to unrealistic predictions when one applies the Michigan Lyman model parameters for hypofractionation regimens of a dose per fraction much greater than 1.5 Gy. We then, in this study, use Parameter Set I for $d \leq 3$ Gy and Parameter Set II for a higher doses per fraction when designing new dose fractionation regimens based on Lyman model NCTP calculations. Eq. (6) is applied to normalize a dose distribution to 1.5 Gy or 4.6 Gy per fraction depending on which parameter set is used.

Individualized treatment planning

The NTCP is the endpoint for liver treatment planning. We first decide a NCTP limit and a dose per fraction for a given patient. We then determine a maximum tolerable dose (MTD) based on the normal liver DVH of the patient. Finally a biologically effective dose (BED) corresponding to the MTD is calculated by $BED = (1+\frac{d}{\alpha/\beta})D - \gamma T/\alpha$ with derived radiobiologic parameters, and the expected patient survival rate can be obtained in our model.

RESULTS

The results from fittings of Eq. (1) and Eq. (2) to clinical survival data are shown in Figs. 1 and 2, respectively. In the fitting, we assume dose homogeneity over the target, as all the data are from three-dimensional conformal radiation therapy. The parameters obtained from the fitting are listed in Table 2. The designations α/β and T_d from the two fittings are almost the same. The extracted α values from two fitting functions are different, which implies that the α value depends on the function forms from which it is extracted. In addition, magnitudes of the obtained α are small, compared with those from *in vitro* measurements (26, 27). For *in vitro* tumor cell culture, average values of α are about 0.5 Gy^{-1} and 0.2 Gy^{-1} for radiosensitive tumor cells and radioresistant

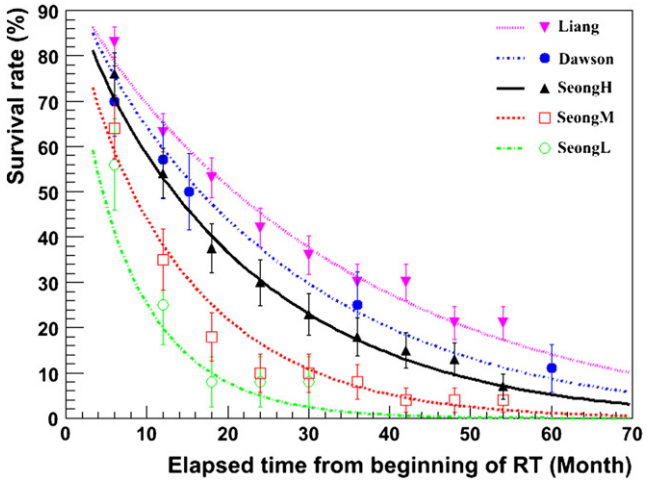

Fig. 1. Fitting results using Eq. (1). Data from Seong *et al.* (6) are divided into three dose bins: Seong H (D > 50 Gy), Seong M (D = 40–50 Gy), and Seong L (D < 40 Gy). Data points labeled by Liang *et al.* (10), and Dawson *et al.* (8, 9), respectively.

tumor cells, respectively. However the extracted α values for liver tumors are similar to those obtained in studying survival rates of brain tumor patients (22). A similar discrepancy was also seen for breast cancer. For five different breast cancer cell lines, α values ranging from 0.12–0.54 Gy^{-1} were obtained (28), whereas $\alpha = 0.06$ Gy^{-1} was extracted from clinical data for breast cancer (29). It was suggested (30) that this discrepancy may be solved using a Gaussian distribution of α values for the population of patients. For prostate cancer, α was found to be 0.19 Gy^{-1} from *in vitro* data and 0.15 Gy^{-1} from *in vivo* data (31). However the other investigators extracted different *in vivo* α values of 0.04 Gy^{-1} (32) and 0.036 Gy^{-1} (33). It is still under debate whether radiobiologic parameters obtained *in vivo* are consistent with ones obtained *in vitro* for prostate (34). It implies that radiobiologic parameters derived from *in vitro* tumor cell cultures may not be directly useful in clinic even if a correlation

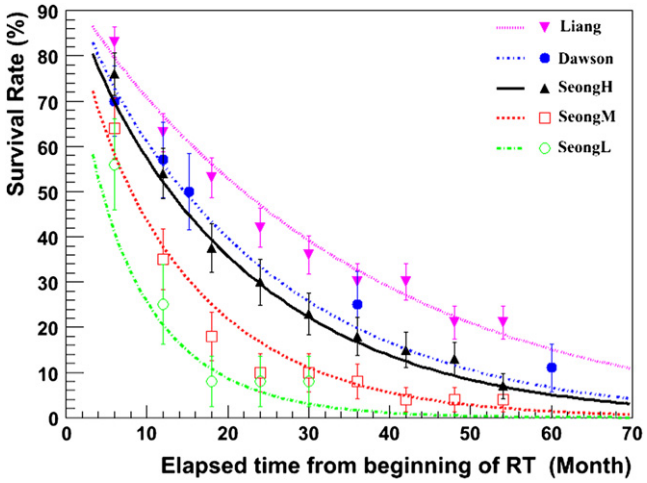

Fig. 2. Fitting results using Eq. (2). as the fitting function with K given by Eq. (3). Data from Seong *et al.* (6) are divided into three dose bins: Seong H (D > 50 Gy), Seong M (D = 40–50 Gy), and Seong L (D < 40 Gy). Data points labeled by Liang *et al.* (10), and Dawson *et al.* (8, 9), respectively.

Table 2. Fitting parameters obtained from Eq. (1) (Fitting I) and Eq. (2) (Fitting II)

Fitting I		Fitting II	
K	$(4.2 \pm 0.7) \times 10^{-2}$	K_{50}/K_0	2.03 ± 0.04
α	0.037 ± 0.006 (Gy^{-1})	α	0.010 ± 0.001 (Gy^{-1})
α/β	14.3 ± 2.0 (Gy)	α/β	15.0 ± 2.0 (Gy)
T_d	114 ± 11 day	T_d	128 ± 12 day
a	1268 ± 184 (mo^{-1})	σ_k/K_0	0.65 ± 0.06
δ	0.16 ± 0.01	δ	0.20 ± 0.01
χ^2/dof	0.6	χ^2/dof	0.7

Errors are standard deviations.

between intrinsic radiosensitivity of human cell lines and radioresponsiveness of human tumors exists. The potential doubling time, T_d, obtained in our study is around 120 days. The potential doubling time for HCC patients was reported in Cucchetti *et al.* (35) and Sheu *et al.* (36) by imaging tumor growth, where T_d was found to be 80 days (35) and 117 days (36), respectively. We are not aware of α and α/β for liver tumors being previously extracted from clinical patient data.

The parameter, δ, is ~0.2, indicating a slowing down of tumor growth with time. Such a behavior of tumor growth has been known for a long time and is usually called the Gompertz tumor growth model (37). The Gompertz model describes tumor growth by nonlinear differential equations and is much more complicated than the model that we propose here. However our model produces general characteristics of the Gompertz model, *i.e.,* a tumor could initially show accelerated growth, then the tumor growth decelerates after a time lapse. The Gompertz model can be understood by the fact that nutrients from the vascular supply cannot support the rapid growth of a tumor when its size is over a critical volume. The purpose of this article is not to investigate the dynamics of tumor growth but, rather, to fit clinical survival data to extract radiobiologic parameters for primary liver tumors. Therefore we are satisfied to use the simple term $(\gamma(\tau - T))^{\delta}$ for the description of tumor regrowth after radiation treatments. However an exponential function is applied for the tumor growth during the treatment interval, since radiation may cause a tumor to shrink and allow the tumor to grow.

Figures 1 and 2 show that Eq. (1) and Eq. (2) can fit clinical survival data almost equally well. The designations χ^2/dof are 0.6 and 0.7 for Fitting I and Fitting II, respectively. We can apply either of them to estimate the patient survival rate for a given dose fractionation scheme. In the rest of this study, the parameters from Fitting II will be used for calculations.

The survival rates for 1, 2, 3, and 4 years as a function of BED calculated with Eq. (2) are plotted in Fig. 3. The BEDs obtained for Liang *et al.* (10), Dawson *et al.* (8, 9), and Seong *et al.* (6) are 56 Gy, 45 Gy, 42 Gy, 30 Gy, and 16 Gy, respectively. Figure 3 enables us to determine easily the expected survival rate for a patient under a given radiation treatment plan.

Next we are going to design a series of dose fractionation regimens using NTCP as an endpoint. That is, the maximum

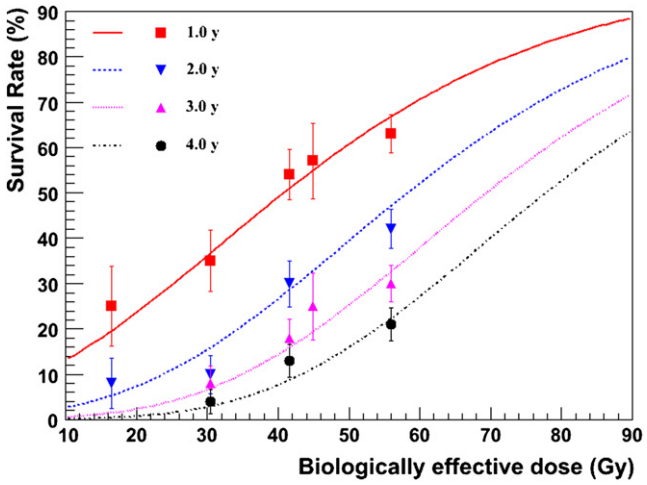

Fig. 3. Survival rates at 1, 2, 3, and 4 years as a function of biologically effective dose. Data points are the same as those in Figs. 1 and 2 for 1, 2, 3, and 4 years.

tolerable dose is determined based on a clinically acceptable NTCP limit. The expected patient survival rates can then be obtained from Fig. 3 based on a calculation of BED. This approach is justified because the Lyman model parameters applied were obtained from the same patient data that were used to derive the model parameters in Table 2.

In Table 3, 11 dose fraction regimens are listed. The regimens, marked by *, are those recommended in RTOG 0438. Other regimens produce nearly the same tumor BED as that for the proven dose fractionation regimen (*BED* = 45 Gy at 1.5 Gy/fx and 10 fractions per week (8)). For a given total fraction N and treatment time T, the dose per fraction d, which generates the desired *BED*, can be calculated through

$$Nd + \frac{N}{\alpha/\beta}d^2 - \frac{\ln 2}{\alpha T_d}T = BED \qquad (7)$$

with a solution

$$d = \frac{-N + \sqrt{N^2 + \frac{4N}{\alpha/\beta}\left(\frac{\ln 2}{\alpha T_d}T + BED\right)}}{\frac{2N}{\alpha/\beta}}$$

The NTCP for three effective volumes (35%, 40% and 45%) are calculated for those regimens in Table 4. The reason for doing these calculations for V_{eff} bins is to avoid the use of the normal liver DVH, which is patient specific. The Lyman model Parameter Set I is used for the calculations of Regimens 1 and 2. The Lyman model Parameter Set II is used for the rest of the regimens. A 10% NTCP limit is applied for dose escalation (5). MTD for 10% NTCP at V_{eff} = 45% are obtained. The new treatment time and the tumor BED corresponding to these MTD are also listed in Table 4. Finally survival rates at 1 year for each escalated regimen are given in the last column of Table 4. V_{eff} = 45% was selected to do these calculations because it represents an average of the effective volumes (38).

From results in Tables 3 and 4, it is clear that for the general population of primary liver patients with an effective volume of ~ 45% (*1*), the RTOG 3.5-Gy regimen has a substantially lower tumor BED, (*2*) total doses for all RTOG regimens can be escalated to achieve higher BED and survival rates, with NTCP <10%, and (*3*) regimens with a dose per fraction of 3.5–5 Gy lead to the best 1-year survival rates of ~ 80%.

DISCUSSION

In this study, reported clinical data from three institutions were analyzed. We have tried to select data from patient groups with a similar mean tumor size. However variation exists among patient population from different institutions in terms of tumor staging, normal liver function, treatment methods other than RT, and so on. These factors affect patient survival in addition to the prescription dose and the dose per fraction. Moreover differences in dose prescription method, target volume definition, and treatment technique would also affect the comparability of data from various institutions.

The question is, How sensitive our extracted radiobiologic parameters against these variations? To test this issue, we apply our model to fit survival rate data from Wu *et al.* (7). These data are collected from three dose fractionation

Table 3. Hypofractionation regimens and tumor biologically effective dose (BED)

Regimen	Dose/fx (Gy)	Fraction per wk	Total fraction	Pres. dose (Gy)	Treatment time (days)	Tumor BED (Gy)
1	1.9	5	33	62.7	45	46.3
2	2.8	3	21	58.8	47	44.3
3*	3.5	5	10	35.0	12	36.7
4	3.7	3	13	48.1	29	44.3
5*	4	5	10	40.0	12	44.2
6*	4.5	5	10	45.0	12	52.0
7*	5	5	10	50.0	12	60.2
8	4.8	2	10	48.0	33	45.5
9	5.4	2	8	43.2	26	44.7
10	8.8	1	4	35.2	21	44.5
11	19.7	1	1	19.7	1	45.0

* Regimens are as recommended by Radiation Therapy Oncology Group 0438. The rest of the regimens are designed to have the same BED of 45 Gy. Because of the roundup error of the dose per fraction listed in Column 2, the actual BED values in the last column are slightly different from 45 Gy.

Table 4. Dose escalation for the dose fractionation regimens of Table 3 based on calculations of normal tissue complication probability (NTCP) and maximum tolerable dose (MTD), and expected survival rates at 1 year

	NTCP (%)						
Regimen	V_{eff}(%) = 35	V_{eff}(%) = 40	V_{eff}(%) = 45	MTD (10% NTCP V_{eff} = 45% (Gy)	Treatment time (days)	Tumor BED (Gy)	SR(1y)% at MTD
1	0.1	1.0	5.7	65.4	47	48.2	59
2	1.3	8.4	29.8	53.2	43	39.9	49
3*	0.3	0.4	0.6	74.6	30	75.8	82
4	0.8	1.3	2.1	71.9	45	65.3	75
5*	0.5	0.8	1.3	68.3	24	73.5	80
6*	1.0	1.6	2.6	63.1	19	71.7	79
7*	1.8	3.2	5.3	58.6	16	69.5	77
8	1.4	2.4	4.0	60.4	44	55.9	67
9	1.3	2.2	3.7	55.4	37	55.3	66
10	2.5	4.4	7.4	37.9	29	44.4	54
11	3.9	7.0	11.8	18.8	1	41.8	48

Abbreviation: SR 1y = expected survival rates at 1 year.

* Regimens are as recommended by Radiation Therapy Oncology Group 0438. The rest of the regimens are designed to have the same biologically effective dose (BED) of 45 Gy. Because of the roundup error of the dose per fraction listed in Column 2, the actual BED values in the last column are slightly different from 45 Gy.

schemes for HCC patients: (*1*) 60 Gy, 7.5 Gy/fx; (*2*) 56 Gy, 6.0 Gy/fx; and (*3*) 48 Gy, 4.0 Gy/fx. Radiation therapy is given 3 days per week. The median tumor size is 10.7 cm, similar to that of patients in Table 1. We did not combine these data with patients in Table 1 because survival rates of these data are recorded from diagnosis rather than from the beginning of RT. In addition to that, three-dimensional conformal radiation therapy was started 3 to 4 weeks after TACE. Because of that, time dependence of survival curves in Wu *et al.* (7) would be different from those recorded from the beginning of RT.

Because these data are from the same institution, however, variability of patient selection is minimized. Our interest is to extract radiobiologic parameters α, α/β and T_d. These parameters are sensitive to the dependence of survival curves on the prescription dose and the dose per fraction, unlike the other parameters in our model, K_{50}/K_0, δ and σ_k/K_0, which are more sensitive to time dependence of survival curves.

The fitting results of Eq. (2) to Wu's data are shown in Fig. 4. The extracted parameters are $\alpha = 0.011 \pm 0.001$, $\alpha/\beta = 14.7 \pm 2.0$, $T_d = 103 \pm 8$, $K_{50}/K_0 = 2.25 \pm 0.18$, $\sigma_k/K_0 = 0.44 \pm 0.06$, and $\delta = 0.28 \pm 0.03$. Compared with the parameters in Table 2, the radiobiologic parameters are unchanged within statistical uncertainties. Differences are seen for the other parameters as expected. In this fitting, we have assumed a 2-month interval between diagnosis and beginning of RT. The fitting quality is not as good as that in Fig. 2 with a $\chi^2/dof = 2.0$, which may be caused by the fact that a constant shift of 2 months would not make the survival curves equal to those recorded from beginning of RT. These results show that our extracted radiobiologic parameters for primary liver tumors are robust as long as data are not from the patient population specially selected based on prognostic factors that affect patient survival. However the model formalism needs to be modified if the follow-up time does not start from the beginning of RT.

If our model is used to fit data from such a selective sample, we do expect changes of radiobiologic parameters. Figure 5 shows a fitting to survival data from T3 and T4 stage patients (10). Because there are so few data points from this dose fractionation regimen, we fix the other fitting parameters to be the values listed in Table 2 except K_{50}/K_0 and α. The fitting results are $K_{50}/K_0 = 2.12 \pm 0.09$, $\alpha = 0.0105 \pm 0.0004$ for T3 patients and $K_{50}/K_0 = 1.90 \pm 0.09$, $\alpha = 0.0088 \pm 0.0004$ for T4 patients. These results seem to show that a T4 liver tumor has a smaller K_{50}/K_0 ratio and is less sensitive to radiation in comparison to a T3 liver tumor.

Because of limited liver patient data, this study includes patient populations from three institutions. These patients had a median tumor size of 8 to 10 cm. Because tumor size

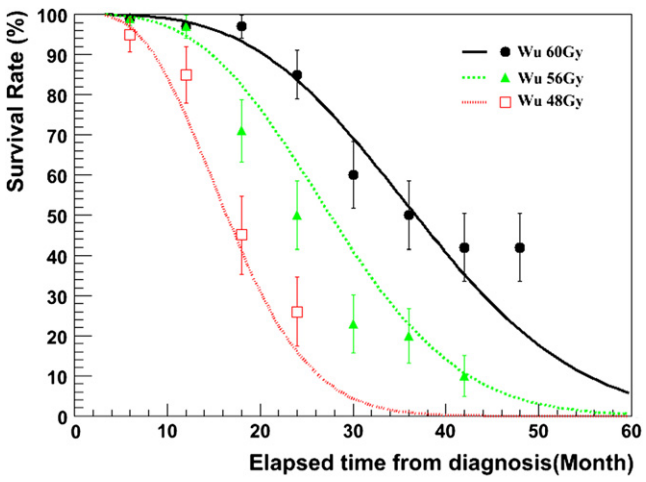

Fig. 4. Fitting of Eq. (2) to data from Wu *et al.* (7). The doses per fraction for these data are Wu 60 Gy: 7.5 Gy/fx, Wu 56 Gy: 6.0 Gy/fx, and Wu 48 Gy: 4.0 Gy/fx. Note that follow-up time of the survival data starts from diagnosis. A transformation of $(\gamma(\tau - T))^{\delta}$ to $(\gamma(\tau - T - 2))^{\delta}$ is applied in Eq. (3), assuming an interval of 2 months between diagnosis and the beginning of radiation therapy.

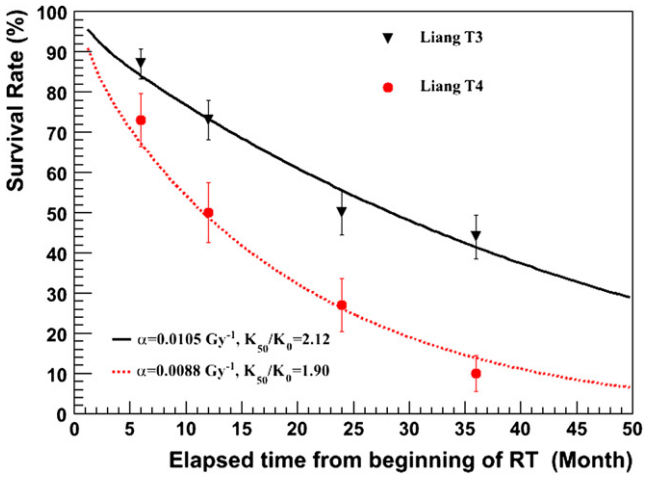

Fig. 5. Fitting of Eq. (2) to data from Liang *et al*. (10) for patients with T3 and T4 liver tumors.

greatly affects patient survival and NTCP for normal liver, the results obtained from this study should not be used for a patient group with a very different median tumor size. In addition the radiobiologic parameters in this report were extracted from a general population of liver patients with a mix of liver function scores, tumor staging, and concurrent treatment modalities, and should not be applied to a patient group specially selected based on such criteria as liver function scores and tumor staging. For concurrent treatments such as TACE and Fluorodeoxyuridine, their effects on the radiation treatment outcome are still under debate. Unlike factors such as tumor size, dose, and staging, there is no clear evidence that TACE and Fluorodeoxyuridine are significant factors affecting patient survival (1). However the methods of this study are general. One could derive a new set of parameters for a specific patient group at interest if patient data were available. In addition new data may also be used to verify whether the current formalism needs to be modified.

Another weakness of the current study is the use of median values of prescribed dose, fraction dose, and treatment time instead of clinical data from individual patients, because these data for each patient are not available in published articles. Such an approach may affect accuracy of the extracted model parameters when the ranges of prescribed dose, fraction dose, and treatment time are large. In addition patient-specific factors influencing outcome cannot be included in this method. If individual patient data are available, a maximal likelihood method (19) should be used to extract model parameters.

This study is based on the assumption that a dose fractionation scheme is a significant factor for survival of primary liver cancer patients. Eventually the assumption must be tested by randomized clinical trials. In this paper clinical data from three institutions were applied, which unavoidably introduces patient heterogeneities. Even with the study shown in Fig. 4, the patient heterogeneities may still exist because the selection of a patient into a particular dose fractionation scheme could be correlated with other prognostic factors. More data, especially data from randomized clinical trials, will be helpful to resolve this issue in the future.

The results in Table 4 were obtained based on an assumption that the biologically equivalent dose of a fractionation scheme with respect to the reference fractionation scheme can be calculated using Eq. (6), which is commonly used in literature. We do not know exactly when the equation breaks down for a dose per fraction very much different from d_{ref}. Our choice of 3 Gy per fraction as a threshold for using Parameter Set II seems arbitrary. However the expected NTCP for a prescription dose of 53.6 Gy as in Liang *et al*. (10) at V_{eff} = 45% using Parameter Set I is 43% for 3.5 Gy per fraction, which is disproved by the measured NTCP (10) at a similar dose per fraction. Therefore we chose 3 Gy per fraction as the threshold based on our understanding on this issue.

Caution is therefore needed when using the results of Table 4 in the dose fractionation region not covered by the current clinical data. However Table 4 provides guidance on how to calculate expected patient survival using NTCP as an endpoint. With more NTCP data for liver patients at various hypofractionated schemes, we will be able to establish more robust relationship of NTCPs between two fractionation schemes.

CONCLUSION

Using the model that we developed for survival rate calculations, a set of plausible radiobiologic parameters for liver tumors was derived from published clinical data. The reliability of these parameters was tested with two fitting functions and different patient data sets. Based on the newly derived parameters, a series of hypofractionated treatment regimens were designed to increase patient survival rates while keeping the NTCP under control. With caution, these parameters may be useful in understanding the liver tumor irradiation response to a particular dose fractionation scheme, and may be applied when designing individualized treatment planning for liver tumor patients.

REFERENCES

1. Ben-Josef E, Lawrence TS. Radiotherapy for unresectable hepatic malignancies. *Semin Radiat Oncol* 2005;15:273–278.
2. Tsuzuki T, Sugioka A, Ueda M. Hepatic resection for hepatocellular carcinoma. *Surgery* 1990;107:511–520.
3. Nagorney DM, van Heerden JA, Ilstrup DM, *et al*. Primary hepatic malignancy: Surgical management and determinants of survival. *Surgery* 1989;1067:740–748.
4. Hashimoto T, Tokuuye K, Fukumitsu N, *et al*. Repeated proton therapy for hepatocellular carcinoma. *J Radiat Oncol Biol Phys* 2006;65:196–202.
5. Ben-Josef E, Normolle D, Ensminger WD, *et al*. Phase II trial of high-dose conformal radiation therapy with concurrent hepatic artery floxuridline for unresectable intrahepatic malignancies. *J Clin Oncol* 2005;23:8739–8747.

6. Seong J, Park HC, Han KH, Chon CY. Clinical results and prognostic factors in radiotherapy for unresectable hepatocellular carcinoma: A retrospective study of 158 patients. *J Radiat Oncol Biol Phys* 2003;55:329–336.
7. Wu DH, Liu L, Chen LH. Therapeutic effects and prognostic factors in three-dimensional conformal radiotherapy combined with transcatheter arterial chemoembolization for hepatocellular carcinoma. *World J Gastroenterol* 2004;10:2184–2189.
8. Dawson LA, McGinn CJ, Normolle D, *et al*. Escalated focal liver radiation and concurrent hepatic artery fluorodeoxyuridine for unresectable intrahepatic maglignancies. *J Clin Oncol* 2000; 18:2210–2218.
9. Hawkins MA, Dawson LA. Radiation therapy for hepatocellular carcinoma from palliation to cure. *Cancer* 2006;106: 1653–1663.
10. Liang SX, Zhu XD, Lu HJ, *et al*. Hypofractionated three-dimendional conformal radiation therapy for primary liver carcinoma. *Cancer* 2005;103:2181–2188.
11. Liu MT, Li SH, Chu TC, *et al*. Three-dimensional conformal radiation therapy for unresectable hepatocellular carcinoma patients who had failed with or were unsuited for transcatheter arterial chemoembolization. *Jpn J Clin Oncol* 2004;34: 532–539.
12. Guo WJ, Yu EX. Evaluation of combined therapy with chemoembolization and irradiation for large hepatocellular carcinoma. *Br J Radiol* 2000;73:1091–1097.
13. Nakagawa K, Yamashita H, Shiraishi K, *et al*. Radiation therapy for portal venous invasion by hepatocellular carcinoma. *World J Gastroenterol* 2005;11:7237–7241.
14. Cheng JC, Chuang VP, Cheng SH, *et al*. Local radiotherapy with or without transcatheter arterial chemoembolization for patients with unresectable hepatocellular carcinoma. *J Radiat Oncol Biol Phys* 2000;47:435–442.
15. Herfarth KK, Debus J, Lohr F, *et al*. Stereotactic single-dose radiation therapy of liver tumors: Results of a phase I//II trial. *J Clin Oncol* 2001;19:164–170.
16. Kim TH, Kim DY, Park JW, *et al*. Three-dimensional conformal radiotherapy of unresectable hepatocellular carcinoma patients for whom transcatheter arterial chemoembolization was ineffective or unsuitable. *Am J Clin Oncol* 2006;29:568–575.
17. Mornex F, Girard N, Beziat C, *et al*. Feasibility and efficacy of high-dose three-dimensional-conformal radiotherapy in cirrhotic patients with small-size hepatocellular carcinoma noneligible for curative therapies—mature results of the French phase II RTF-1 trial. *Int J Radiat Oncol Biol Phys* 2006;66: 1152–1158.
18. Katz AW, Dawson LA, Elsaleh H, *et al*. A phase I trial of highly conformal radiation therapy for patients with liver metastases. Radiation Therapy Oncology Group 0438. Accessed at http://www.rtog.org.
19. Dawson LA, Normolle D, Balter JM, *et al*. Analysis of radiation-induced liver disease using the Lyman NTCP model. *J Radiat Oncol Biol Phys* 2002;53:810–821.
20. Xu ZY, Liang SX, Zhu J RD, *et al*. Prediction of radiation-induced liver disease by Lyman normal-tissue complication probability model in three-dimensional conformation radiation therapy for primary liver carcinoma. *Int J Radiat Oncol Biol Phys* 2006;65:189–195.
21. Sachs RK, Hahnfeldt P, Brenner DJ. The link between low-LET dose-response relations and the underlying kinetics of damage production/repair/misrepair. *Int J Radiat Biol* 1997; 72:351–374.
22. Qi XR, Schultz CJ, Li XA. An estimation of radiobiological parameters from clinical outcomes for radiation treatment planning of brain tumors. *Int J Radiat Oncol Biol Phys* 2006;64: 1570–1580.
23. Webb S, Nahum AE. A model for calculating tumor control probability in radiotherapy including the effects of inhomogeneous distributions of dose and clonogenic cell density. *Phys Med Biol* 1993;38:653–666.
24. Mathew A, Pandey M, Murthy NS. Survival analysis: Caveats and pitfalls. *Eur J Surg Oncol* 1999;25:321–329.
25. Stavrev P, Hristov D, Field C, *et al*. Fractionation correction to Lyman's model. *Med Phys* 2002;29. 1248–1248.
26. Fertil B, Malaise EP. Intrinsic radiosensitivity of human cell lines is correlated with radioresponsiveness of human tumors: Analysis of 101 published survival curves. *Int J Radiat Oncol Biol Phys* 1985;11:1699–1707.
27. Deacon JM, Peckham MJ, Steel GG. The radioresponsiveness of human tumors and the initial slope of the cell survival curve. *J Radiother Oncol* 1984;2:317–323.
28. Ruiz de Almodovar JM, Nunez MI, McMillan TJ, *et al*. Initial radiation-induced DNA damage in human tumor cell lines: A correlation with intrinsic cellular radiosensitivity. *Br J Cancer* 1994;69:457–462.
29. Brenner DJ. Dose, volume, and tumor-control predictions in radiotherapy. *Int J Radiat Oncol Biol Phys* 1993;26:171–179.
30. Webb S. Optimum parameters in a model of tumor control probability including interpatient heterogeneity. *Phys Med Biol* 1994;39:1895–1914.
31. Wang JZ, Stewart RD, Carlson DJ, *et al*. Comments on the ''Comparison of *in vitro* and *in vivo* α/β ratios for prostate cancer.'' In response to Drs. Daşu and Fowler. *Phys Med Biol* 2005; 50:L5–L8.
32. Fowler JF, Chappell RJ. Ritter MA Is α/β for prostate tumors really low? *Int J Radiat Oncol Biol Phys* 2001;50:1021–1031.
33. Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. *Int J Radiat Oncol Biol Phys* 1999; 43:1095–1101.
34. Dasu A, Fowler JF. Comments on the ''Comparison of *in vitro* and *in vivo* α/β ratios for prostate cancer.'' *Phys Med Biol* 2005; 50:L1–L4.
35. Cucchetti A, Vivarelli M, Piscaglia F, *et al*. Tumor doubling time predicts recurrence after surgery and describes the histological pattern of hepatocellular carcinoma on cirrhosis. *J Hepatol* 2005;43:310–316.
36. Sheu JC, Sung JL, Chen DS, *et al*. Growth rate of asymptomatic hepatocellular carcinoma and its clinical implication. *Gastroenterology* 1985;89:259–266.
37. Speer J, Petrosky V, Retsky M, *et al*. A stochastic numerical model of breast cancer growth that simulates clinical data. *Cancer Res* 1984;44:4124–4130.
38. Dawson LA, Eccles C, Craig T. Individualized image guided iso-NTCP based liver cancer SBRT. *Acta Oncol* 2006;45: 856–864.