Biologically Equivalent Dose in Construction of Tumor Control Probability Curve for Hepatocellular Carcinoma Treated by Radiotherapy

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Abstract

Background: The incorporation of biologically effective dose (BED) or equivalent total dose in 2 Gy fraction (EQD_2) in tumor control probability (TCP) equation allows the fitting of clinical data to yield a mathematical function useful for predicting outcome of dose-fractionation.

Purpose: To establish a logistic function describing the dependence of TCP on BED or EQD_2 for hepatocellular carcinoma (HCC) treated by radiation and to evaluate the validity BED- and EQD_2-derived functions in predicting effects of dose-fractionations particularly those relevant to stereotactic body radiotherapy (SBRT).

Methods and Materials: Eight clinical papers published during 2000 and 2008 were selected for fitting. Dose and dose per fraction were converted to BED and EQD_2 with an α/β of 10 Gy for HCC. These biologically equivalent doses and their associated survival rate at 2 years were fitted to a logit-transformed equation. The difference between slopes of logit-regression lines was analyzed by t-test. The parameters of fit were used for defining the logistic functions which were used to calculate TCPs for dose-fractionation schemes typically used in SBRT.

Results: Two significant logit-transformed regression lines were established ($P = 0.0119$) and enabled the construction of two TCP curves described by following logistic functions:

$$TCP_{BED} = \frac{\exp [4.9392-0.0596\ BED]}{1 + \exp-[4.9392-0.0596\ BED]}$$

$$TCP_{EQD2} = \frac{\exp-[4.9403\ -\ 0.0716\ EQD_2]}{1 + \exp-[4.9403\ -\ 0.0716\ EQD_2]}$$

The r^2 for the curve fitting was 0.83. The established functions were used to calculate TCP for series of fractionation schemes relevant to SBRT and this allowed paper-based study of dose escalation and pre-clinical evaluation of the chosen scheme for treatment of HCC with SBRT. Neither slopes of two curves nor TCPs calculated by BED and EQD_2 were statistically different ($P > 0.5$). Validity of TCP prediction was supported by published data on treatment of HCC with SBRT.

Conclusion: BED- or EQD_2-derived logistic function is equally reliable in predicting effects of dose-fractionations for HCC particularly those typically used in SBRT.

Introduction

Hepatocellular carcinoma (HCC) is a prominent problem of the Eastern world.1 Liver resection and transplantation are optimal therapies for HCC. However, more than 80% of patients with HCC are unsuitable for surgery due to tumor multifocality, impaired liver function and /or involvement of vascular or biliary structures[2]. Historically, radiation therapy (RT) played a minor role in management of unrespectable HCC because of the low tolerance of whole liver irradiation. Technologic advancements including three - dimensional (3-D) planning techniques to deliver high doses that tightly conform to the tumor target; image-guided RT to localize tumor at the time of treatment; tumor immobilization and /or tracking to account for respiratory related organ motion, make possible the delivery of far higher doses to HCC than what was achievable previously with a low risk of hepatic texicity[2]. Focally high-dose RT alone or in combination with transarterial chemoembolization (TACE) has been used ever since to treat HCC.

Regarding to RT alone, many investigators had shown that three dimensional conformal radiotherapy (3D-CRT) which employed conventional dose fraction of 1.8-2 Gy permitted tumor dose escalation to induce significantly higher response rate 3-6 than what could be expected from traditional whole-liver external beam radiotherapy (EBRT)[7]. Recently, stereotactic body radiotherapy (SBRT), a novel RT modality with the implementation of high-end technology to achieve the extremely high accuracy in tumor dose delivery without damaging surrounding normal tissues, is characterized by the use of a few ablative-dose fractions, i.e. 3-5 fractions of at least 10 Gy per fraction, over shorter period of total treatment time[8]. The local control of lung cancer treated with SBRT has been higher than previous RT modalities[9]. Limited data are documented for treatment of primary liver cancer with SBRT[10-12]. Most initial efforts focused on the management of liver metastases[9] with histology other than HCC.

As HCC is one of the most common malignancies in Asian countries, the interest in employing SBRT in management of primary liver cancer is high. Delivery the ablative-dose fractionation by SBRT means a more biologically potent schedule, i.e. higher BED, is prescribed and hence higher tumor control rate can be expected. At the same physical dose of 48 Gy delivered in 6 Gy per fraction by SBRT and 2 Gy per fraction by 3D-CRT, SBRT induced a 2-year survival rate of 39%[10] in contrast to the 19.9% by 3D-CRT[3]. Despite this improvement in tumor control, optimal SBRT dose-fractionation for HCC remains to be established. Most previous studies[10,11] used 6 Gy per fraction which is lower than the fraction size of 10Gy or more suggested on the basis of lung cancer treatment[8].

Tumor control probability (TCP) based on the linear-quadratic (LQ) model and Poisson statistics can be presented as a function of biologically equivalent dose, i.e. BED (biologically effective dose)[13] or EQD_2 (equivalent total dose in 2 Gy fraction)[14]. This allows the fitting of clinical data to obtain a dose-response relationship which is well simulated by a logistic function depicted by an S-shaped curve. The dose-response function will serve as an effective tool for calculation of dose-fractionation at a chosen TCP or vice versa and has been used for pre-clinical assessment of the effectiveness of SBRT schedules in treatment of lung cancer[14]. The aims of this study were 1. to compare the logistic functions predicting the TCP of HCC established by fitting BED and EQD_2 data, 2. to evaluate the validity of BED- and EQD_2-derived functions in prediction of TCP for fractionation schedule employing large dose fractions typically used in SBRT.

Methods and Materials

Clinical data

A systemic literature search was conducted using the MEDLINE data base and secondary references from review articles on radiotherapy of HCC. This study included English-language articles that reported a 2-year survival rate for primary HCC either treated by conventional EBRT or 3D-CRT or SBRT. The exclusion criteria were hepatic metastases, primary HCC treated by combined radiation and TACE. A total of 8 articles were eligible for this study (Table 1).

Radiobiologically equivalent doses and tumor control probability

Linear-quadratic (LQ) model and biologically effective dose (BED) BED, a concept commonly used to compare different fractionation regimes and to design new treatment schedule, can be described by the following equations[14]:

$$BED = -\frac{\ln S}{\alpha} = D(1 + d/\alpha/\beta) \quad (1)$$

$$\ln S = -\alpha BED \quad (2)$$

$$S = e^{-\alpha BED} \quad (3)$$

Equivalent total dose in 2 Gy fraction (EQD_2)

The concept of EQD_2 or NTD (normalized total dose as termed by Fowler[14]) allows a straight-forward comparison of different fractionation schedules, from which the total doses and doses per fraction are converted to EQD_2 (equation 5). By this approach, the schedule associated with greater EQD_2 will be more effective than the one with smaller EQD_2.

$$EQD_2(1 + 2/\alpha/\beta) = D(1 + d/\alpha/\beta) = BED \quad (4)$$

$$EQD_2 = \frac{D(d + \alpha/\beta)}{(1 + 2\alpha/\beta)} \quad (5)$$

$$EQD_2 = \frac{BED}{(2 + \alpha/\beta)} \quad (6)$$

Different dose fractionation schedules as shown in Table 1 were converted to BED and EQD2 using equations 1 and 5 or 6. The α/β for HCC for is 10 Gy[14].

Tumor control probability (TCP) Analytically, TCP incorporates the LQ function for cell survival (S) to describe tumor cure when all clonogenic cells (M) have been eradicated.

$$TCP = \exp[MS] \quad (7)$$

Substitute equations 3 to equation 7 obtained

$$TCP_{BED} = \exp[M.\exp(-\alpha BED)] \quad (8)$$

Substitute equation 6 to equation 8 yielded

$$TCP_{EQD2} = \exp\{-M.\exp[-\alpha(1 + 2\alpha/\beta) EQD2]\} \quad (9)$$

TCP described by the logistic function It has been widely accepted that TCP can be simulated by the logistic function.

$$TCP_{BED} = \frac{\exp[a + b\,BED]}{1 + \exp[a + b\,BED]} \quad (10)$$

or

$$TCP_{EQD2} = \frac{\exp[a' + b'\,EQD2]}{1 + \exp[a' + b'EQD_2]} \quad (11)$$

By logit transformation, equations 10 and 11 could be linearized as follows :

$$\ln\left(\frac{TCP_{BED}}{1 - TCP_{BED}}\right) = a + b\,BED \quad (12)$$

and

$$\ln\left(\frac{TCP_{EQD2}}{1 - TCP_{EQD2}}\right) = a' + b'EQD_2 \quad (13)$$

TCP curve fitting Since the size of dose per fraction is the factor governing the fractionation effect, a schedule is considered different on the basis of fraction size. For a certain dose per fraction, different total doses (because of different fraction numbers) were averaged arithmetically while the associated TCPs were weighted and summed up as follow[14].

$$TCP_{weighted}(\%) = \frac{1}{N}\sum_{i=1}^{N} n_i TCP_i \quad (14)$$

where n_i was the number of patients treated in series i and N was the total number of patients treated with the same dose per fraction. The biologically equivalent dose, BED or EQD_2, and its associated TCP were fitted to equations 12 and 13, respectively. The parameters of fit were used for the construction of TCP curve.

Statistical analysis

The logit fit of TCP versus BED or EQD_2 were performed by the least squares method. The strength of the straight-line fit was assessed by the coefficient of determination or r^2. Two-tailed t-test was used for analyzing the significance of the logit-regression line and also used for testing the difference between two slopes. Statistically significant difference was decided when $P \leq 0.05$.

Table 1 Results of radiotherapy in treatment of hepatocellular carcinoma.

Investigator	Treatment modality	Mean tumor diameter (cm)	Number treated	Dose per fraction (Gy)	Mean total dose (Gy)	Survival rate at 2 years(%)
Cheng, et al [7]	EBRT	10.3	17	1.8 - 2	46.9	13
Park, et al [3]	3D-CRT	8.9	158	1.8	48.2	19.9
Liu, et al [4]	3D-CRT	7.68	44	1.8	50.4	40.3
Kim, et al [5]	3D-CRT	11.5	27	2 - 3	47.68	20.7
Liang, et al [6]	3D-CRT	9.57	80	4.88	53.6	42
Taguchi, et al [10]	SBRT	3.6	15	6	48	39
Tse, et al [11]	SBRT	6.91	31	6	36	12.25
Romero, et al [12]	SBRT	3.5	3	5	25	
			1	10	30	40
			4	12.5	37.5	

Results

Clinical data used for fitting TCP curves were obtained from 8 papers[3-6,7,10-12] describing the treatment of primary HCC with EBRT[7], 3D-CRT[3-6] and SBRT10-12 (Table 1). All of these reports provide 2-year survival rates. Some reported outcomes of RT and RT + TACE[7], only result of RT was extracted for the analysis. Data from RT + TACE were excluded on the ground that TACE might affect radiation response. Our preliminary analysis of combined RT and TACE data failed to demonstrate the significant dependence of TCP on BED or EQD_2. Another report presented outcomes of treatment for primary HCC and liver metastases[12], data pertaining to metastases were excluded. The average tumor size in patients treated by conventional fractionation scheme (1.8 - 2 Gy per fraction) was 9.59 cm and the size for those treated by hypofractionation was 4.67 cm. In curve fitting, dose homogeneity was assumed over the tumor target as 95.53% (363 out of 380) of total cases were treated by 3D-CRT and SBRT. Dose and dose per fraction in Table 1 were converted to BED and EQD_2 with an α/β of 10 Gy for HCC[14]. Although an α/β of 15 Gy was determined for HCC by Tai et al[13], this estimate was derived from patients treated by RT as well as combined RT and TACE. This might not truly reflect the radiation response of HCC. Our preliminary analysis of RT + TACE data revealed no significant dose-response relationship.

Table 2 Logit parameters for Figure 1 fitted with data in Table 1.

Parameter of fit	TCP_{BED}	P - value	TCP_{EQD2}	P - value
Slope (95% CI)	0.0596	0.0119	0.0716	0.0119
	(0.0218 - 0.0974)		(0.0262 - 0.117)	
Intercept (95% CI)	- 4.9392	0.0052	- 4.9403	0.0052
	(- 7.4112, - 2.4672)		(-7.4143, - 2.4662)	
R - squared	0.8275	-	0.8273	-

No statistically significant difference between slopes of TCP_{BED} and TCP_{EQD2} regression lines ($P > 0.5$).

BED or EQD_2 with its associate 2-year survival rate (or termed as TCP in this analysis) were fitted to equations 12 and 13. The parameters of fit are shown in Table 2. Significant regression lines were observed for both curve fittings (P = 0.0119). A relatively high r^2 of 0.83 was observed either for BED- or EQD_2-derived TCP. Slope of EQD_2 fit was higher than that of BED, i.e. 0.0716 and 0.0596, respectively. However, no statistically significant difference could be confirmed (P > 0.5). Two logistic curves describing the dependence of 2-year survival rate on BED or EQD_2 were constructed using parameters of fit as shown in Table 2. Two S-shaped TCP curves are shown in Figure 1. The S-shaped curves symbolized the logistic function and that indicated the correctness of using this mathematical function in fitting HCC data.

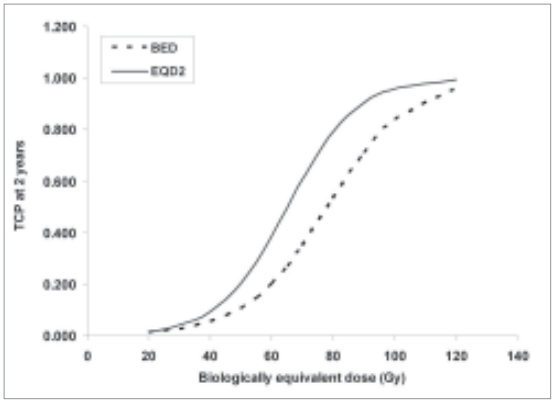

Figure 1 Survival rate at 2 years as a function of biologically equivalent dose. The curves are constructed using the parameters of fit as shown in Table 2.

Based on these mathematical functions, the 2-year survival rate of HCC was calculated to help understanding the effect of dose escalation on TCP. Dose-escalation had been performed by increasing fraction number until reaching a saturation response of ≥ 90% (Figure 1). From the calculated data, a dose of 8 Gy per fraction was impractical for SBRT since it required 9 fractions to achieve a 2-year survival rate of 94.23% (data are not shown) while 10 Gy per fraction would required only 6 fractions. Increasing size of dose per fraction would make the radiation dose more biologically potent as fewer fractions were required to reach saturation response, for instance 4 fractions for 15 Gy per fraction and 2 fractions for 20 Gy per fraction. It was clear from this

prediction that a single dose was ineffective in tumor control since a single dose of 23 Gy could only induce a 2-year survival rate of 39.85%. No calculation for dose fraction greater than 23 Gy was attempted since this would violate the validity of LQ model (Table 3). Nevertheless at a single dose of 26 Gy prescribed by some investigators[15], an overestimated survival rate of 65.85% was obtained. This was far below the saturation level.

Table 3 EQD_2, BED and two-year survival rate (%) calculated for typical fractionation schemes used in SBRT.

Dose per fraction (Gy)		Number of fraction						
		1	2	3	4	5	6	7
8	EQD_2 (Gy)	12	24	36	48	60	72	84
	TCP_{EQD2} (%)	1.66	3.84	8.61	18.19	34.43	55.35	74.54
	BED (Gy)	14.4	28.8	43.2	57.6	72	86.4	100.8
	TCP_{BED} (%)	1.66	3.83	8.59	18.15	34.34	55.24	74.43
10	EQD_2 (Gy)	16.67	33.33	50	66.67	83.33	100	116.67
	TCP_{EQD2} (%)	2.31	7.22	20.42	45.84	73.62	90.20	96.81
	BED (Gy)	20	40	60	80	100	120	140
	TCP_{BED} (%)	2.30	7.21	20.37	45.73	73.51	90.14	96.79
12	EQD_2 (Gy)	22	44	66	88	110	-	-
	TCP_{EQD2} (%)	3.34	14.31	44.65	79.58	94.96	-	-
	BED (Gy)	26.4	52.8	79.2	105.6	132	-	-
	TCP_{BED} (%)	3.34	14.28	44.55	79.49	94.92	-	-
15	EQD_2 (Gy)	31.25	62.5	93.75	125	-	-	-
	TCP_{EQD2} (%)	6.28	38.57	85.47	98.22	-	-	-
	BED (Gy)	37.5	75	112.5	150	-	-	-
	TCP_{BED} (%)	6.27	38.48	85.39	98.20	-	-	-
18	EQD_2 (Gy)	42	84	126	-	-	-	-
	TCP_{EQD2} (%)	12.64	74.54	98.34	-	-	-	-
	BED (Gy)	50.4	100.8	151.2	-	-	-	-
	TCP_{BED} (%)	12.62	74.43	98.32	-	-	-	-
20	EQD_2 (Gy)	50	100	150	-	-	-	-
	TCP_{EQD2} (%)	20.42	90.2	99.7	-	-	-	-
	BED (Gy)	60	120	180	-	-	-	-
	TCP_{BED} (%)	20.37	90.14	99.69	-	-	-	-
23	EQD_2 (Gy)	63.25	126.5	-	-	-	-	-
	TCP_{EQD2} (%)	39.85	98.4	-	-	-	-	-
	BED (Gy)	75.9	151.8	-	-	-	-	-
	TCP_{BED} (%)	39.76	98.33	-	-	-	-	-

The validity of TCP prediction was evaluated by comparing our calculations with the treatment outcomes of a few relevant studies[15-18] (Table 4). Good agreement between model prediction and clinical observation suggested the validity of the logistic functions established by this study.

Table 4 Comparison the two-year survival rate from published reports with the rate calculated by the EQD2-derived TCP.

Investigator	No.of lesions treated	Treatment	Survival rate at 2 years (%)	
			Previous study	This study prediction
Herfath, et al 2001,[15] 2004[16]	60	14 Gy x 1 to 26 Gy x 1	Not available but many tumors recurred 2-3 years later.	5.04 % to 65.58 %
Wada, et al 2004[17]	42	15 Gy x 3	88.6 %	85.47 %
Wulf, et al 2006[18]	56	7 Gy x 4 (n = 1) 10 Gy x 3 (n = 27) 12-12.5 x 3 (n = 19) 26x1 (n = 9)	32 %	35.73 %

Discussion

With the highly precise and efficient nature of SBRT in delivery a few fractions of biologically potent doses to tumor target without exceeding the tolerance of normal liver makes possible to treat HCC for cure, an aim which was previously considered difficult to achieve. The first report for SBRT in treatment of HCC was published in 1995[19]. No standard protocol for ablative-dose fractionation has been proposed to date. The dose per fraction in previous studies varied from 5 to 26 Gy in 1 to 6 fractions19. Most SBRT data included in this study, i.e. 85.19% of a total of 54 cases, were from 6 Gyx6 and 6 Gyx8 schedules. Compilation of clinical data is a slow process because of long follow-up time. Fowler et al[14] constructed a TCP curve defined by the logistic function for non-small-cell lung cancer using data from dose escalation study conducted at the University of Michigan[20]. This allowed the pre-clinical evaluation of typical SBRT schedules[14].

In this study, we were able to establish a significant logistic function to describe the dependence of TCP (2-year survival rate) on BED or EQD_2 using data from 8 publications. No correction for tumor repopulation during treatment was performed since HCC has a long potential doubling time of 128 days[13]. Eighty-three percent of the data could be explained by the fitted logit regression line (i.e. $r^2 = 0.83$). This might be criticized on the

inclusion of 14.21% of 380 subjects with smaller tumors (d < 7.5 cm) in the analysis, while majority of cases (85.79%, 326/380) had tumors of greater than 7.5 cm in diameter. In fact, it was the inclusion of data from smaller tumors that made possible the establishment of the dose-response relationship. Nevertheless, an r^2 of 0.83 justified a reasonable fit. Concerning the shape of the TCP curve, the curve defined by EQD_2 displayed a better S-shape, hence better discriminating capability between dose-proportional response and treatment saturation region. The curve reached a plateau at survival rate of 90%. With the flatter TCP curve for BED, its discrimination power was lower. The curve failed to reach asymptote and that this made the identification of saturation response almost impossible. TCP defined by BED as $\exp[-M.\exp(-\alpha BED)]$, in fact is equal to $\exp\{ M.\exp[-\alpha (1+ 2/10) EQD_2]\}$. This implies that slope of TCP_{BED} curve is 1.2 folds less than slope of TCP_{EQD2} curve. By calculation, a 1.2 fold difference in slopes was obtained to support this notion. Besides the visual difference in shapes of two curves, no significant difference could be demonstrated for the two logistic functions either by comparing slopes of the two logit-regression lines or TCPs calculated by these two equations. EQD_2 was preferred over BED since it was easier to interpret.

The established logistic functions were validated against published data which were available only for a few numbers. A publication by Wada et al[17] on the treatment of pulmonary and hepatic tumors with 3D-CRT using 15 Gy x 3 fractions, they observed an overall survival-rate at 2-year of 83.6%. By our prediction, the TCP was 85.47%. Wulf et al[18] treated 5 patients with primary HCC and 34 patients with 51 hepatic metastases with several fractionation schemes, i.e. 7 Gy x 4 (n = 1), 10 Gy x 3 (n = 27), 12 - 2.5 Gy x 3 (n = 19) and 26 Gy x 1 (n = 9). An overall 2-year survival-rate was 32% for all patients. The corresponding survival rates by our calculation were 10.91%, 20.42%, 44.65% and 65.57%, respectively. These figures when weighted by the number of lesions treated, we obtained an average of 35.73% which was in good agreement with the clinical observation despite the TCP associated with the 26 Gy fraction might be overestimated. Theoretically, LQ model can over-predict the effect at high dose because of curve bending, a graphical behavior which is not supported by any experimental data[8]. To what extent the LQ model can correctly predict the survival function is a subject of recent interest particularly by those who use ablative-dose fractionation like SBRT. Brenner[21] has defended the validity of the LQ model up to 10 Gy per fraction and suggests that the model is still reasonable for the use up to 18 Gy per fraction. This limit is even raised up to 23 Gy by Fowler based on his study of epithelial tissue of the skin14. On

this basis, we performed a paper-based study of the effect of dose-escalation by calculating the TCP upon increasing fraction number starting from a dose of 8 Gy per fraction up to 23 Gy per fraction.

In conclusion, two significant logistic functions describing the dependence of TCP or 2-year survival rate on EQD_2 or BED have been established for HCC. The two functions are equivalent and are used for the construction of TCP curves. Validity of the model prediction for TCP is verified by outcomes of some relevant clinical trials. These mathematical functions serve as an effective tool for paper-based studying the effect of dose-escalation and for pre-clinical evaluation of the SBRT regimes chosen for HCC.

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