IS THE LINEAR-QUADRATIC MODEL APPROPRIATE FOR STEREOTACTIC IRRADIATION OF METASTATIC BRAIN TUMORS?

TADASHI YOSHIMINE and NOBUMASA FUJITANI
Department of Radiation Oncology, Nara Medical University
Central Division of Radiology, Nara Medical University Hospital

TOSHITAKA IKEGUCHI and HIROSHI IWAMI
Central Division of Radiology, Nara Medical University Hospital

RYOSUKE MATSUDA
Department of Neurosurgery, Nara Medical University

TETSURO TAMAMOTO, YOKO MORIMOTO and MASATOSHI HASEGAWA
Department of Radiation Oncology, Nara Medical University

Received March 28, 2018

Abstract:The biologically effective dose (BED) based on the linear-quadratic (LQ) model has been commonly used to evaluate the dose-effect relationships among the different fractionation schedules, but whether the LQ model is appropriate for hypofractionated (HF) high-dose stereotactic irradiation (STI) is uncertain. The validity of the model at high doses per fraction has been critically examined. In this study, STI of metastatic brain tumors was evaluated to suggest the applicability of the LQ model to HF high-dose radiotherapy. No significant difference was found between stereotactic radiosurgery (SRS) and HF stereotactic radiotherapy (SRT) in the analyses of 151 tumors. Furthermore, no significant differences were found among SRS, HF-SRT, and non-HF SRT in 117 metastatic lung adenocarcinomas. The results of this study suggest that BED calculation is a reasonable approach for careful dose-effect evaluation based on the LQ model for HF high-dose radiotherapy for metastatic brain tumors, especially lung adenocarcinomas.

Key words: LQ model, BED, stereotactic irradiation, SRS, SRT

Introduction

The biologically effective dose (BED) based on the linear-quadratic (LQ) model has been most commonly used to evaluate dose effect to compare different fractionation schedules in radiotherapy1-6). The basic LQ equation and BED calculation formula are as follows:

$E = \alpha d + \beta d^2, nE = n(\alpha d + \beta d^2)$

$\mathrm{BED} = nE/\alpha = nd(1 + d/\alpha/\beta)$,

where E is the effect per fraction, BED is the biologically effective dose, n is the fraction number, d is the fraction size, α and β are constants, and α/β is the α/β ratio.

The efficacy and validity of the LQ model for various fractionation schedules in recent high-precision radiotherapy are often discussed[4-6]. Whether the LQ model is appropriate for hypofractionated (HF) high-dose stereotactic irradiation (STI), stereotactic radiosurgery (SRS), or stereotactic radiotherapy (SRT) is uncertain. The validity of the model at high doses per fraction has been critically examined[7]. The possibility of additional effects resulting from endothelial cell damage, enhanced tumor immunity, or stem cell damage has been suggested to account for the superior effect of single-fraction SRS[8, 9]. In contrast, fractionated SRT has been suggested to be more effective than SRS in other studies[6, 10].

In the present study, the relationships among the different fractionation schedules for STI of metastatic brain tumors were evaluated to suggest the applicability of the LQ model to HF high-dose radiotherapies such as SRS and SRT.

Materials and Methods

The radiation treatment plans for metastatic brain tumors treated with STI in our institute between March 2006 and May 2014 were reviewed. To evaluate treatment response, treatment plans for 151 tumors in 52 patients with follow-up of at least 3 months were included. In this study, the stereotactic treatment plans were classified into three groups as follows: SRS, single high-dose irradiation with a fraction size of $\geq$ 12-Gy; HF-SRT, hypofractionated irradiation with a fraction size of >4 Gy; non-HF SRT (NHF-SRT), fractionated irradiation with a fraction size of $\leq$ 4 Gy.

Radiation treatment planning was performed with a pencil beam algorithm using Brain Scan and iPlan (BrainLab, Feldkirchen Germany), and radiotherapy was administered using 6-MV X-rays (Novalis, BrainLab).

The BED for each tumor was calculated using the LQ equation and BED calculation formula to compare the differences among the three groups. An alpha-to-beta ratio of 10 was used for LQ-model and BED calculation (BED10), and ratios of 5 and 15 were also used in some analyses (BED5 and BED15). Changes in tumor volume were evaluated using 1.5-T magnetic resonance imaging performed during the follow-up after the irradiation (Magnetom Symphony 1.5 T, Siemens, Erlangen, Germany). The cumulative probabilities of the partial response rates (PRRs) and Kaplan-Meier plot of local disease control (LDC) were estimated as a function of day after the initial treatment with SRS, HF-SRT, or NHF-SRT for metastatic brain tumors. The groups were compared using the log-rank test.

Results

The characteristics of the 52 patients with metastatic brain tumors and the prescribed doses of SRS, HF-SRT, and NHF-SRT are shown in Table 1. The characteristics of the tumors and the number of tumors in each treatment group are shown in Table 2. Most of the cases were lung adenocarcinomas, and approximately 70% of the tumors (107/151) were treated with SRS.

The comparison of PRRs as a function of day after the initial treatment with SRS, HF-SRT, or NHF-SRT for all 151 metastatic brain tumors is shown in Fig. 1. The PRRs of SRS and HF-SRT

Table 1. Characteristics of the patients with metastatic brain tumors treated with stereotactic radiosurgery (SRS), hypofractionated stereotactic radiotherapy (HF-SRT), or non-hypofractionated SRT (NHF-SRT)

Patients (M/F)	52 (28/24)		
	SRS	HF-SRT	NHF-SRT
Gender (M/F)	14/15	13/8	8/4
Age , median (y)	64.0	63.8	67.4
(range)	(46.8–79.1)	(56.1–80.6)	(44.0–79.1)
Prescribed doses			
Median	22Gy	30Gy/5Fr	30Gy/10Fr
(range)	(12Gy–25Gy)	(30Gy/5Fr–35Gy/7Fr)	(50Gy/25Fr–35Gy/7Fr)

Table 2. Characteristics of the tumors treated with stereotactic radiosurgery (SRS), hypofractionated stereotactic radiotherapy (HF-SRT), or non-hypofractionated SRT (NHF-SRT)

	SRS	HF-SRT	NHF-SRT
Primary site			
Lung	95	28	8
Colon	4	0	1
Breast	6	3	1
Other	2	1	2
Total	107	32	12
Pathology			
Adenocarcinoma	85	21	11
Small cell carcinoma	2	2	1
Non Small cell carcinoma	17	7	0
Squamous cell carcinoma	3	2	0
PTV volume median (mm^3) (range)	0.26 (0.01–4.11)	3.07 (0.17–21.97)	0.34 (0.01–7.02)

were significantly better than that of NHF-SRT ($p < 0.05$). No significant difference in PRR was found between SRS and HF-SRT.

Comparison of PRRs as a function of day after the initial treatment with SRS, HF-SRT, or NHF-SRT for metastatic brain tumors in an equivalent BED10 level (55 Gy ≤ BED10 < 65 Gy) is shown in Fig. 2. The PRRs of SRS and HF-SRT were significantly better than that of NHF-SRT ($p < 0.05$). No significant difference in PRR was found between SRS and HF-SRT.

The Kaplan-Meier plot of LDC as a function of day after the initial treatment with SRS, HF-SRT, or NHF-SRT for all 151 metastatic brain tumors is shown in Fig. 3. SRS and HF-SRT showed significantly better LDC than NHF-SRT ($p < 0.05$). No significant difference in LDC was found between SRS and HF-SRT.

The Kaplan-Meier plot of LDC as a function of day after the initial treatment with SRS, HF-SRT, or NHF-SRT for metastatic brain tumors in an equivalent BED10 (55 Gy ≤ BED10 < 65 Gy) is shown in Fig. 4. SRS and HF-SRT showed better effect in terms of LDC than NHF-SRT, but this was not statistically significantly. No significant difference in effect was found between SRS and HF-SRT.

The Kaplan-Meier plot of LDC as a function of day after the initial treatment with SRS, HF-SRT, or NHF-SRT for 117 metastatic lung adenocarcinomas is shown in Fig. 5. No significant differences were found among SRS, HF-SRT, and NHF-SRT.

The Kaplan-Meier plot of LDC as a function of day after the initial treatment with SRS, HF-SRT, or NHF-SRT for metastatic lung adenocarcinomas in an equivalent BED10 (55 Gy ≤ BED10 < 65 Gy) is shown in Fig. 6. No significant differences were found among SRS, HF-SRT, and NHF-SRT.

In addition to the aforementioned analyses, comparison of PRRs and LDC in equivalent BED5 (55 Gy ≤ BED10 < 65 Gy) and BED15 (55 Gy ≤ BED10 < 65 Gy) resulted in similar results, respectively (data not shown).

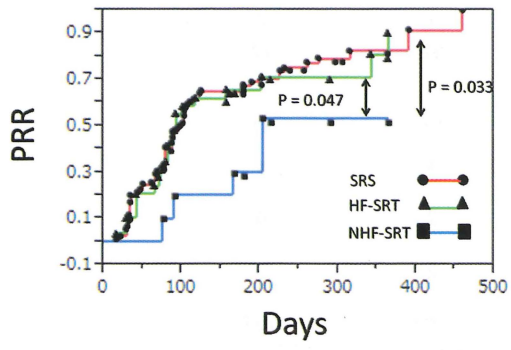

Fig. 1. Comparison of partial response rates (PRRs) as a function of day after the initial treatment with stereotactic radiosurgery (SRS), hypofractionated stereotactic radiotherapy (HF-SRT), or non-hypofractionated SRT (NHF-SRT) for all 151 metastatic brain tumors.

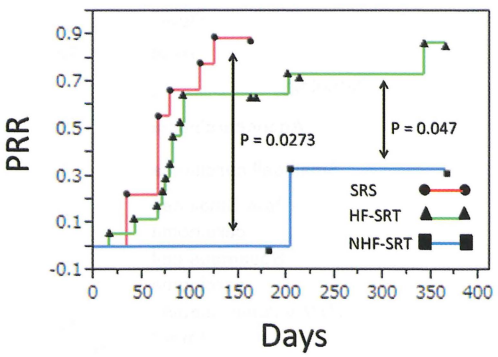

Fig. 2. Comparison of partial response rates (PRRs) as a function of day after the initial treatment with stereotactic radiosurgery (SRS), hypofractionated stereotactic radiotherapy (HF-SRT), or non-hypofractionated SRT (NHF-SRT) for metastatic brain tumors in an equivalent BED10 (55 Gy ≤ BED10 < 65 Gy).

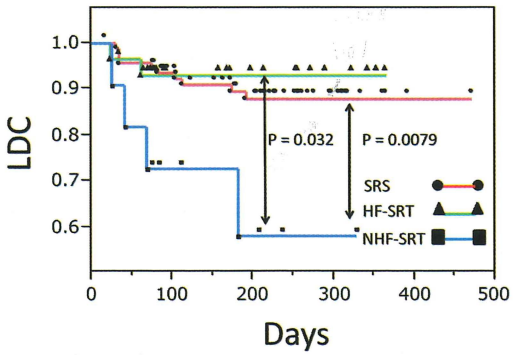

Fig. 3. Kaplan-Meier plot of local disease control (LDC) as a function of day after the initial treatment with stereotactic radiosurgery (SRS), hypofractionated stereotactic radiotherapy (HF-SRT), or non-hypofractionated SRT (NHF-SRT) for all 151 metastatic brain tumors.

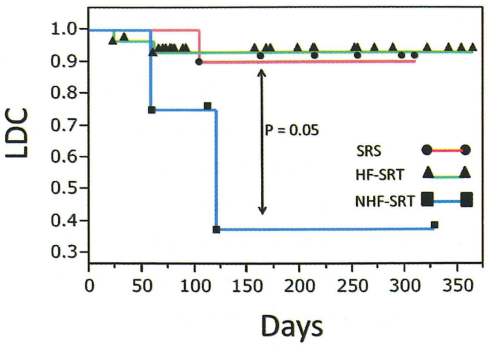

Fig. 4. Kaplan-Meier plot of local disease control (LDC) as a function of day after the initial treatment with stereotactic radiosurgery (SRS), hypofractionated stereotactic radiotherapy (HF-SRT), or non-hypofractionated SRT (NHF-SRT) for metastatic brain tumors in an equivalent BED10 (55 Gy ≤ BED10 < 65 Gy).

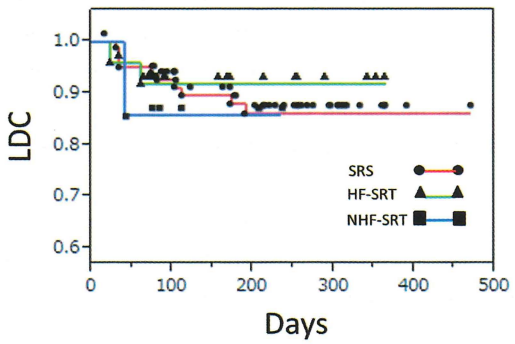

Fig. 5. Kaplan-Meier plot of local disease control (LDC) as a function of day after the initial treatment with stereotactic radiosurgery (SRS), hypofractionated stereotactic radiotherapy (HF-SRT), or non-hypofractionated SRT (NHF-SRT) for 117 metastatic lung adenocarcinomas.

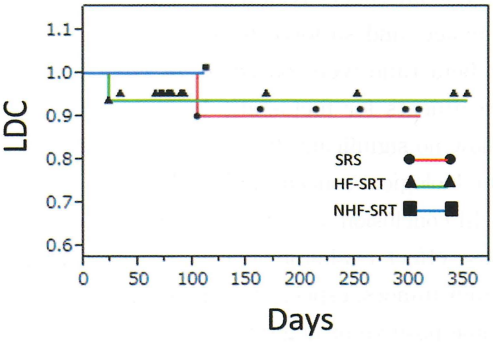

Fig. 6. Kaplan-Meier plot of local disease control (LDC) as a function of day after the initial treatment with stereotactic radiosurgery (SRS), hypofractionated stereotactic radiotherapy (HF-SRT), or non-hypofractionated SRT (NHF-SRT) for metastatic lung adenocarcinomas in an equivalent BED10 (55 Gy ≤ BED10 < 65 Gy).

Discussion

In the present study, treatment responses to the radiation treatment plans for 151 brain metastases were evaluated to suggest the applicability of the LQ model and BED to HF high-dose radiotherapy by considering the isoeffective dose. No significant differences were found between SRS and HF-SRT in the analyses of all 151 tumors. Furthermore, no significant differences were found among SRS, HF-SRT, and NHF-SRT in the analyses of 117 metastatic lung adenocarcinomas.

The alpha-to-beta ratios in the LQ model were usually suggested to be >8 Gy, but in some

tumors, this was <5 Gy[11,12]. However, tumors available for LQ model calculation based on an *in vivo* study are limited[3,11]. Most of the available data are obtained by *in vitro* studies at doses lower than those used in SRS[8], and caution against using *in vitro* cell survival data for α / β ratio determination was suggested[13]. An alpha-to-beta ratio of 10 was used for BED calculation in this study, in accordance with that used in previous studies[3, 11]. In addition, ratios of 5 and 15 were used in some analyses to determine the effect of differences in alpha-to-beta ratio, considering the previous discussions. BED5, BED10, and BED15, calculated using ratios of 5, 10, and 15, respectively, showed similar curves. The differences among the ratios of 5, 10, and 15 had little impact on the results.

In the biological basis of radiotherapy, 5 factors (5 Rs) are suggested to be critical in determining the net effect of radiotherapy on tumors. These factors are as follows: repair of sublethal damage, repopulation after radiation, redistribution within the cell cycle, reoxygenation, and (intrinsic) radiosensitivity[14, 15]. Brown et al. suggested that the radiobiology concepts of the 5 Rs are sufficient to explain the clinical data for most tumors. The data obtained from clinical studies were the result of the much larger BEDs delivered via SRS and SBRT[9]. The validity of the LQ model at high doses per fraction has been critically examined[7], and the possibility of additional effects resulting from endothelial cell damage, enhanced tumor immunity, stem cell damage, and so forth have been frequently discussed[8, 9]. Most of the available data on alpha-to-beta ratio were based on *in vitro* studies, and most of the clinical data were derived from treatments for metastatic brain tumors or early-stage non-small cell lung cancer[6]. Our data show no significant differences between SRS and HF-SRT, and support the clinical usefulness of the biological concept and model[16].

In conclusion, this study suggests that it will be reasonable to use BED calculation for careful dose-effect evaluation based on the LQ model for HF high-dose radiotherapy for metastatic brain tumors, especially lung adenocarcinomas, in clinical practice, considering the possibility of some positive or negative additional effects.

Ethical Statement

This study was approved by the institutional ethics committee of Nara Medical University.

References

1) Withers HR, Thames HD Jr, Peters LJ. : A new isoeffect curve for change in dose per fraction. Radiother. Oncol. **1** : 187–91, 1983.
2) Fowler JF. : Fractionated radiation therapy after Strandqvist. Acta. Radiol. Oncol. **23** : 209–16, 1984.
3) Fowler JF. : Review : total doses in fractionated radiotherapy–implications of new radiobiological data. Int. J. Radiat. Biol. Relat. Stud. Phys. Chem. Med. **46** : 103–20, 1984.
4) Mohan R, Wu Q, Manning M, Schmidt–Ullrich R. : Radiobiological considerations in the design of fractionation strategies for intensity–modulated radiation therapy of head and neck cancers. Int. J. Radiat. Oncol. Biol. Phys. **46** : 619–30, 2000.
5) Nahum AE. Nahum AE. : The radiobiology of hypofractionation. Clin. Oncol. (R. Coll. Radiol.) **27** : 260–9, 2015.

6) Shuryak I, Carlson DJ, Brown JM, Brenner DJ. : High-dose and fractionation effects in stereotactic radiation therapy : Analysis of tumor control data from 2965 patients. Radiother. Oncol. **115** : 327-34, 2015.

7) Kocher, M. , Treuer, H. , Voges, J. , Hoevelsb, M. , Sturmb,V., MuÈllera, R. : Computer simulation of cytotoxic and vascular effects of radiosurgery in solid and necrotic brain metastases. Radiother. Oncol. **54** : 149-156, 2000.

8) Kirkpatrick, J. P. Meyer, J. J. and Marks, L. B. : The Linear-quadratic model is inappropriate to model high dose per fraction effects in radiosurgery. Semin. Radiat. Oncol. **18** : 240-243, 2008.

9) Brown JM, Carlson DJ, Brenner DJ. : The tumor radiobiology of SRS and SBRT : are more than the 5 Rs involved? Int. J. Radiat. Oncol. Biol. Phys. **88** : 254-62, 2014.

10) Otsuka S, Shibamoto Y, Iwata H, Murata R, Sugie C, Ito M, Ogino H. : Compatibility of the linear-quadratic formalism and biologically effective dose concept to high-dose-per-fraction irradiation in a murine tumor. Int. J. Radiat. Oncol. Biol. Phys. **81** : 1538-43, 2011.

11) Williams MV, Denekamp J, Fowler JF. : A review of alpha/beta ratios for experimental tumors : implications for clinical studies of altered fractionation. Int. J. Radiat. Oncol. Biol. Phys. **11** : 87-96, 1985.

12) Brenner DJ, Martinez AA, Edmundson GK, Mitchell C, Thames HD, Armour EP. : Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio) , similar to late-responding normal tissue. Int. J. Radiat. Oncol. Biol. Phys. **52** : 6-13, 2002.

13) Garcia, L. M. , Wilkins, D.E. and Raaphorst, G. P. : α / β ratio : A dose range dependence study. Int. J. Radiat. Oncol. Biol. Phys. **67** : 587-593, 2007.

14) Withers, H.R. : The four R's of radiotherapy. in : A.H. Lett JT (Ed.) Advances in Radiation Biology. Vol 5. Academic Press, New York, p241-271, 1975.

15) Steel, G.G., McMillan, T.J., and Peacock, J.H. : The 5Rs of radiobiology. Int. J. Radiat. Biol. **56** : 1045-1048, 1989.

16) Brenner, D. J. : The linear-quadratic model is an appropriate methodology for determining isoeffective doses at large doses per fraction. Semin. Radiat. Oncol. **18** : 234-239, 2008.