Grid therapy: impact of radiobiological models on calculation of therapeutic ratio

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Abstract— **The purpose of this study is evaluation of the impact of radiobiological models in therapeutic ratio (TR) calculation of spatially fractionated (Grid) radiotherapy for different tumor cells. A Monte Carlo technique was employed to calculate the dose distributions of a Grid collimator in a 6 MV beam. The linear-quadratic (LQ) and modified linear quadratic (MLQ) models were used separately to evaluate the therapeutic ratio for different tumor cells (Melanoma, Squamous cell carcinoma (SCC), Adenocarcinoma and Sarcoma). Different maximum dose sizes (10 Gy, 15 Gy and 20 Gy) are considered. For each dose the equivalent uniform dose (EUD) is obtained. The EUDs and TRs for all different doses were derived through the LQ and MLQ models. Calculated therapeutic ratios from two models were compared.**

The results of TRs calculations from both LQ and MLQ have less than 5% difference. EUDs were varied between 2.19 Gy and 3.87 Gy. The TR was dependent on the prescribed dose, cell survival fraction at 2Gy dose (SF2) and radiobiological model parameters.

Keywords— **Grid therapy, Radiobiological models, therapeutic ratio, Monte Carlo simulation.**

I. Introduction

Grid therapy, also known as Spatially fractionated radiation therapy, is a novel technique that has been introduced for treatment of patients with advanced bulky tumors [1]. The required radiation dose is delivered to these patients with standard radiation delivery results in normal cell complications from the surrounding normal tissues [2]. In this technique, an open x-ray radiation field is being converted to a set of pencil beam type radiation fields using an external block which is designed and fabricated from lead or Cerrobend or using the MLC system in the linear accelerators [3]. Different kinds of tumors had been treated using this technique and significant tumor responses have been observed without serious toxicities [4]. The Grid technique was initially proposed to treat deeply seated tumors using orthovoltage machine while avoiding skin toxicity [5]. From that time onward, there are several studies with reported clinical outcome of this radiotherapy methodology using megavoltage linear accelerator. Mohiuddin et al [6] published the results of sixty-one patients that were treated by Grid therapy technique. In their study, good results for the reduction of pain, bleeding control, and tumor volume shrinkage with overall response rate of 91% was observed. Several investigators have used linear quadratic radiobiological model to demonstrate the therapeutic advantages of the Grid therapy [2, 7]. Presently, the most common treatment technique consists of a single fraction of large dose (10-15 Gy) with Grid to the bulky tumors followed by standard radiation therapy [1].

Despite the success of the linear quadratic (LQ) model, for evaluation of the limitation of the Grid therapy with such large doses per fraction still there are challenges that need to be met [8]. Guerrero et al have extended the conventional LQ model with one additional parameter to introduce a modified linear quadratic model (MLQ) which is more prone for the acute high-dose regime [9]. In this study we have applied both LQ and MLQ radiobiological models to calculate therapeutic ratio (TR) of spatially fractionated radiation therapy. This evaluation is performed using Monte Carlo simulation.

II. Methods

In this study the Geant4 [10] (version 9.6.p02) is used to simulate the photon spectrum of a 6 MV x-ray beam emitted by a Varian2100C linear accelerator, based on vendor detailed information. For photon and electron interactions with matter the cross section libraries from Livermore National Laboratory electromagnetic models have been utilized [11]. About 20 million particles were collected in the scoring plane, which was set before the jaws as a phase space file. The phase space file served as a source for simulating the dose distribution in water phantom. A total of 10^6 events are generated to get data with less than 2%/2mm statistical uncertainties. The electron cutoff energy was set to be 1 kev. A voxelized water phantom with overall dimensions of 15×15×15 cm^3 dimension was defined with its center at the isocenter of the machine. Percentage depth dose (PDD) and dose profile of 6MV photon beam were obtained at 5cm depth for 10×10 cm^2 open radiation field size in a water

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phantom. To verify Monte Carlo simulation calculations, these results were compared with the experimental measured data by a calibrated PTW 31010, 0.125 cc Semifelex chamber. For PDD and dose profile calculations the dimensions of each voxel is considered to be 2mm×2mm×2mm. The Grid block with hole-diameter of 1cm and a center-to-center distance of 1.8 cm at the isocenter was also simulated .The Grid pattern was designed to have a hexagonal pattern of circular divergent holes with thickness of 7.5 cm lead, located on the block tray position of the linear accelerator. Figure 1 shows the schematic diagram of the entire pathway of the radiation for simulations in this project.

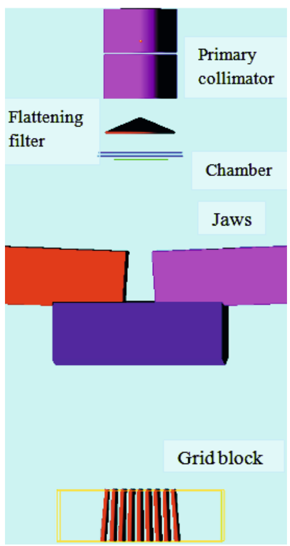

Fig. 1 The schematic diagram of the modeled linear accelerator with a Grid

A dose profile at depth of 5cm in water phantom is used to calculate therapeutic ratio. It has been assumed that the open and shadow area corresponding to each Grid block form a hexagonal shape [12]. Moreover, the volume of tissues receiving nearly identical irradiation under a Grid block was created as circular rings with 1 mm thickness with the volume of Vi. The radiation dose delivered to this segmented volume is D_i . To calculate survival fraction (SF) of Grid therapy, equation 1 and 2 are considered using the LQ and MLQ radiobiological models, respectively, as;

$$SF = \sum V_i \, EXP(-\alpha D_i - \beta D_i^2) \qquad (1)$$

$$SF = \sum V_i \, EXP(-\alpha D_i - g(t)\beta D_i^2) \qquad (2)$$

Where:

$$g(t) = 2(\delta D_i - EXP(-\delta D_i) - 1)/(\delta D_i)^2$$

And,

$$\delta = 2\beta D_0/(1 - \alpha D_0)$$

Where g(t) in equation 2 is the repair rate and dependent on D_0 (The dose to reduce survival to 37%). D is the dose, α and β are LQ parameters. Therapeutic ratios of tumors with different histology (Melanoma, Squamous cell carcinoma (SCC), Adenocarcinoma and Sarcoma) have been calculated using both radiobiological models. Survival fraction of tumors at 2 Gy dose (SF2) and tumors cell lines radiobiological parameters were extracted from published data [11]. The value of α/β ratio for normal cells was considered constant at 2.5 Gy for all calculations. The therapeutic advantage or therapeutic ratio of the Grid therapy was calculated as:

$$TR = \frac{SF_{Grid\ field}^{Norma\ \ tissue}(D)}{SF_{open\ field}^{Norma\ \ tissue}(EUD)} \qquad (3)$$

In addition, various maximum doses (2Gy, 10 Gy, 15 Gy and 20 Gy) are used to evaluate relationship between maximum dose and therapeutic ratio.

III. RESULTS

Figure 2 shows the 2D dose distributions at 5-cm depth for a Grid with 1cm hole-diameter and 1.8 center-to-center distance obtained from Monte Carlo calculations.

Table 1 and 2 shows results for predicting TR at the different prescribed doses using LQ and MLQ models. The difference between the two models is less than 5% for the TR calculations. Equivalent uniform dose (EUD) for all prescribed doses for both models has a value between 2.19 Gy and 3.87 Gy.

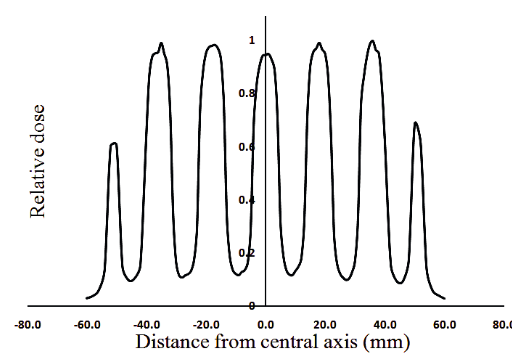

Fig. 2 Beam profile for 6-MV spatially fractionated photon beam at 5 cm depth using Monte Carlo simulation

Table 1 Results for therapeutic ratio (TR) calculations for LQ radiobiological model at different maximum doses

Tumor	*SF2*	*TR (LQ Model)*		
		10Gy	**15Gy**	**20Gy**
Melanoma	0.485	1.22	1.37	1.55
SCC	0.483	1.21	1.37	1.54
Adeno. ca	0.43	1.12	1.23	1.36
Sarcoma	0.42	1.10	1.21	1.33

Table 2 Results for therapeutic ratio (TR) calculations for MLQ radiobiological model at different maximum doses

Tumor	*SF2*	*TR (MLQ Model)*		
		10Gy	**15Gy**	**20Gy**
Melanoma	0.485	1.27	1.42	1.56
SCC	0.483	1.28	1.44	1.60
Adeno. ca	0.43	1.18	1.30	1.40
Sarcoma	0.42	1.15	1.25	1.32

IV. Discussion and conclusion

In this study, we have provided a dosimetric simulation and assessed the therapeutic ratio of Melanoma, SCC, Adenocarcinoma and Sarcoma cells based on two LQ and MLQ radiobilogical models for different doses. Zwicker et al concluded that the therapeutic benefits of Grid therapy is more pronounced for more radioresistant tumor cells [13]. In this study the results of TRs calculations for both radiobiological models indicate increasing the TR value with SF2 and maximum dose value. Recently Zhang et al has compared therapeutic advantages of melanoma cell lines using both linear quadratic (LQ) and modified linear quadratic (MLQ) models and reported insignificant difference in use of two different radiobiological models for Melanoma cells [14]. In this investigation, differences of up to 5% for TR calculations between LQ and MLQ models for four different types of tumor indicate that using radiobiological models that are more appropriate for high dose per fraction would not change the theoretical prediction of spatially fractionated radiotherapy. This is because the value of equivalent uniform dose (EUD) in Grid therapy is in the range that LQ model is valid.

In summary, both the LQ and MLQ models can be used to calculate EUD and TR for Grid therapy. The differences between these two is less than 5%.

References

1. Neuner G. et al. (2012) High-Dose spatially fractionated grid radiation therapy (SFGRT): A comparison of treatment outcomes with cerrobend Vs.MLC SFGRT. . Int. J. Radiat. Oncol. Biol. Phys 82(5) : 1642–1649.
2. Zhang H.et al. (2006) Dosimetric validation of the MCNPx Monte Carlo simulation for radioiologic studies of megavoltage Grid radiotherapy. Int. J. Radiation Oncology Biol. Phys. 66 (5): 1576-1583.
3. Stathakis S. et al.(2009) Dosimetric evaluation of multi-pattern spatially fractionated radiation therapy using a multi-leaf collimator and collapsed cone convolution superposition dose calculation algorithm. Appl. Radiat. Isot 67(10):1939-1944.
4. Mohiuddin M. et al. (1999) High-dose spatially-fractionated radiation (GRID): a new paradigm in the management of advanced cancers. Int. J. Radiat. Oncol. Biol. Phys 45(3): 721-727.
5. Marks H. (1952) Clinical experience with irradiation through a Grid. Presented in part at the Thirty-Sixth Annual Meeting of the Radiological Society of North America : 338-342.
6. Mohiuddin M. et al. (1996) Spatially Fractionated (grid) Radiation for Palliative Treatment of Advanced Cancer. Radiat Oncol Investi 4(1) : 41-47.
7. Meigooni A.S. et al. (2006) Dosimetric characteristics of a newly designed grid block for megavoltage photon radiation and its therapeutic advantage using a linear quadratic model. Med Phys 33(9): 3165-3173.
8. Park C. et al. (2008) Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy. Int. J. Radiat. Oncol. Biol. Phys 70(3): 847-852.
9. Guerrero M. and Li X.A. (2004) Extending the linear–quadratic model for large fraction doses pertinent to stereotactic radiotherapy. PMB 49(20): 4825-4835.
10. Agostinelli, S. et al. (2003) GEANT4—a simulation toolkit. Nuclear instruments and methods in physics research section A: Accelerators, Spectrometers, Detectors and Associated Equipment 506 (3):250-303.
11. Kadri O, Ivanchenko V.N.et al. (2007) Geant4 simulation of electron energy deposition in extended media. Nucl Instrum Meth B 258 (2): 381-387.
12. Buckey C. et al. (2010) Evaluation of a commercially-available block for spatially fractionated radiation therapy. JACMP 11(3): 3163.
13. Zwicker R.D , Meigooni A., and Mohiuddin M. (2004) Therapeutic advantage of grid irradiation for large single fractions. Int. J. Radiat. Oncol. Biol. Phys 58(4): 1309-1315.
14. Zhang, H. et al. (2014) Impact of dose size in single fraction spatially fractionated (grid) radiotherapy for melanoma. Med phys 41(2): 021727.

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