MATHEMATICAL SIMULATION OF BIOLOGICALLY EQUIVALENT DOSES FOR TOTAL BODY IRRADIATION.

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PURPOSE

The aim of the present study is to show possible changes of total biologically equivalent doses in relation to selected radiobiological factors and physical parameters of radiation.

METHODS

The total body irradiation (TBI) requires large field techniques utilization. It means that patient is placed far from a radiation source. That distance is much greater than in conventional radiotherapy. Let's assume that the standard dose measurement is performed 1 meter from the radiation source and the dose rate at 1 meter is 1 Gy/min. Let's assume further that the source - patient distance for TBI is 4 meters. It gives the dose rate 0.04 Gy/min at 4 meters. If the 4 Gy fraction dose is planned and the dose rate is 0.04, the treatment (irradiation) time is 1 hour 45 minutes. It is known from the literature, that if the fraction time is longer than 15 minutes, sublethal damage time factor should be taken into consideration.

Biologically equivalent doses were calculated on the base of linear quadratic (LQ) formula. Because of routine usage of 2 Gy fraction in teleradiotherapy, total biologically equivalent doses were normalized to that value. The LQ formula was supplemented by the sublethal damages repair factor, because of low dose rate of radiation. Taking into consideration, that total dose of TBI could be delivered during one or many fractions, which means that the treatment time is different, LQ formula was supplemented also by the adjustment to compensate cell repopulation.

In order to describe total, normalized, biologically equivalent dose (DGy2) the following mathematic procedure was implemented:

Well known LQ model

(1) $$DGy2 = D_{tot} * \frac{\alpha/\beta + d_f}{\alpha/\beta + 2} \quad [\text{Gy}]$$

where : DT - total absorbed dose [Gy]; a/b- LQ coefficient [Gy]; df - fraction dose [Gy] was replenished by given by Liversage pattern which specifies radiation treatment time and formula which describes overall radiation treatment time. That pattern defines daily dose required for repopulation compensation.

LQ formula and sublethal damage repair time

The Liversage's formula embraces dose rate of used radiation, treatment time and equivalent number of fractions N:

(2) $$N = \frac{\mu * t}{2 * \left(1 - \frac{1}{\mu * t} * \left(1 - e^{(-\mu * t)}\right)\right)}$$

where: m - is the repair time constant; $$\mu = \frac{\text{Ln}(2)}{\text{T}_r}$$

Tr - being the repair halfe time in hours; t - treatment time of fraction dose in hours.

Given formula has some limitations. It cannot be used when: t=0 and/or m=0.

These limitations are important only from the mathematical, not clinical point of view. It means that the formula does not fulfill boundary conditions.

The fraction dose is connected with dose rate - d [Gy/hour], treatment time of fraction dose - t [hour] and number of fraction - N by the following formula:

(3) $$d_f = \frac{dt}{N} \quad [\text{Gy}]$$

Adding formulas (2) and (3), the pattern for fraction dose which include sublethal damage repair time (Tr) can be formulated as:

(4)

$$d_f = \frac{d*2*\left(1-\frac{1}{\mu*d}*\left(1-e^{(-\mu*t)}\right)\right)}{\mu} \quad [Gy]$$

If the fraction dose calculated by formula (4) is inserted to pattern (1), the formula for normalized total biologically equivalent dose calculation arise. The formula includes sublethal damage repair time. Fraction dose calculated that way is the sublethal damage repair time function, which means that its value depends on sublethal damage repair time.

LQ formula and cell repopulation

Another essential radiobiological factor is the cell proliferation time during radiation treatment. The simplest way of its allowance is calculation of the dose which is 'lost' for daily repopulation compensation. If the daily dose (DR) which compensate repopulation is known, after definite time biologically equivalent total dose should be dimnished by:

(5)

$$D_{RT} = \sum_{i=1}^{i=OTT} D_{Ri} \quad [Gy]$$

where: OTT - overall treatment time [day].

Dose value accounted from formula (5) is subtracted from the dose calculated from pattern (1). That formula allows to calculate normalized, biologically equivalent total dose in relation to sublethal damage repair time and cell proliferation time. It means that the dose is dependent on the factors mentioned above. Consequently, the simulation of different radiotherapy schedules as a function of different values of radiobiological factors and a physical parameter of radiation was further performed. Radiobiological parameters as sublethal damage repair time and repopulation time, and a physical parameter - dose rate - were analysed.

RADIOTHERAPY SCHEDULES

For simulation of biologically equivalent dose values, three different radiotherapy schemes were used. These schemes are shown in Table 1.

Table 1:
Dose rate : 2.4 Gy/h

	df [Gy]	N	DT [Gy]	t [h]	OTT [days]	Week days
Schedule I	9	1	9	3.75	1	1
Schedule II	4.5	2	9	1.88	4	1 &4
Schedule III	3	3	9	1.25	6	1 & 3 & 6

The values of a single fraction dose in relation to sublethal damage repair time and dose rate values are presented in Table 2.

Table 2a: Single dose in TBI = 9 Gy

Tr [hours]	Dose rate in Gy/hour			
	1	2	4	10
6.93	6.81	7.79	8.36	8.74
1.39	3.12	4.82	6.40	7.79
0.17	0.49	0.94	1.78	3.65
0.12	0.33	0.64	1.23	2.72

Table 2b: Single dose in TBI = 9 Gy

Tr [hours]	Dose rate in Gy/hour			
	1	2	4	10
6.93	6.81	7.79	8.36	8.74
1.39	3.12	4.82	6.40	7.79
0.17	0.49	0.94	1.78	3.65
0.12	0.33	0.64	1.23	2.72

Table 2c: Single dose in TBI = 3 Gy

Tr [hours]	Dose rate in Gy/hour			
	1	2	4	10
6.93	2.72	2.86	2.93	2.97
1.39	1.93	2.37	2.66	2.86
0.17	0.46	0.83	1.37	2.09

Single dose values presented in Table 2 (a,b,c) were calculated after the pattern (4). Results indicate that fraction dose value is directly proportional to sublethal damage repair time and dose rate of given radiation.

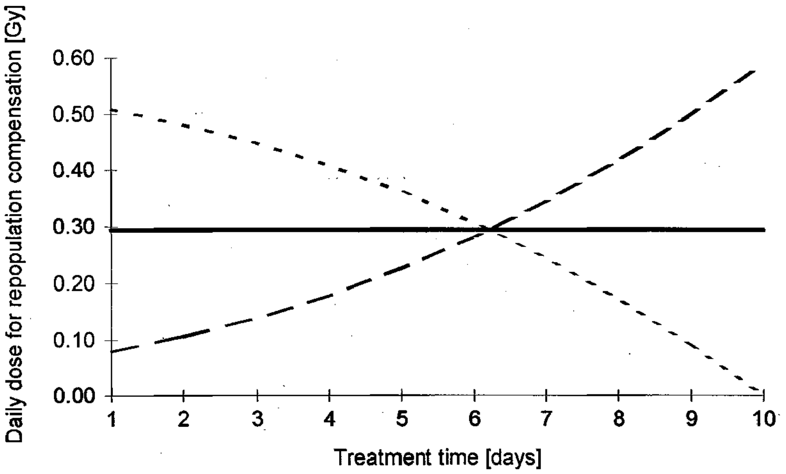

Figure 1 shows hypothetical changes in proliferation time rate during radiation therapy.

The value of total dose which is required for repopulation compensation was calculated after the pattern (5) and is shown in Table 3.

Table 3:

After day	DR CONST	DR GROWS	DR DIMNISCHED
1	0.29 Gy	0.08 Gy	0.51 Gy
4	1.17 Gy	0.50 Gy	1.85 Gy
6	1.76 Gy	1.01 Gy	2.52 Gy

where DR is daily dose for repopulation compensation in Gy.

RESULTS AND DISCUSSION

Table 4 shows normalized total biologically equivalent dose values accounted after pattern (1), that is without taking into consideration sublethal damage repair time and cell repopulation time, for planned 9 Gy total dose.

Table 4.

	a/b=25Gy	a/b=6Gy	a/b=2Gy
Schedule I	11.3 Gy	16.9 Gy	24.8 Gy
Schedule II	9.8 Gy	11.8 Gy	16.6 Gy
Schedule III	9.3 Gy	10.1 Gy	11.3 Gy

Values of normalized biologically equivalent total doses were calculated for earlier defined schedules, for cancer tissues (a/b = 25 Gy), healthy tissues (a/b = 6 Gy) and late responding health tissues (a/b = 2 Gy) Their value for different schedules were in the range of 9.3 Gy - 11.3 Gy for tumour and 11.3 Gy - 24.8 Gy for late responding normal tissues.

When taken into consideration dose rate, sublethal damage repair time and cell proliferation time, normalized total biologically equivalent dose values obtaind are shown in Table 5.

Table 5a:
a/b = 25 Gy

	Schedule I						**Schedule II**						**Schedule III**					
	Dose rate Gy/h						Dose rate Gy/h						Dose rate Gy/h					
	2 Gy/h			4 Gy/h			2 Gy/h			4 Gy/h			2 Gy/h			4 Gy/h		
Tr	DR			DR			DR			DR			DR			DR		
hours	C	D	U	C	D	U	C	D	U	C	D	U	C	D	U	C	D	U
1.4	9.6	9.4	9.9	10.	9.9	10.	8.2	7.6	8.9	8.4	7.4	9.1	7.4	6.6	8.1	7.5	6.7	8.2
0.5	8.8	8.6	9.0	9.3	9.1	9.5	7.8	7.1	8.5	8.1	7.4	8.8	7.1	6.4	7.9	7.3	6.5	8.0
0.2	8.3	8.0	8.5	8.6	8.4	8.5	7.5	6.8	8.1	7.7	7.0	8.4	6.8	6.1	7.6	7.0	6.3	7.8

where: C - cell proliferation is constant, U - cell proliferation increases, D - cell proliferation decreases

Table 5b:
a/b = 2 Gy

	Schedule I		**Schedule II**		**Schedule III**	
	Dose rate		Dose rate		Dose rate	
Tr	2 Gy/h	4 Gy/h	2 Gy/h	4 Gy/h	2 Gy/h	4 Gy/h
1.4 h	18.9	15.3	11.7	12.9	9.8	10.5
0.5 h	13.1	9.61	8.7	10.7	8.1	9.2
0.2 h	8.5	6.63	6.5	8.0	6.4	7.6

On the ground of performed calculations we can state that planned 9 Gy given in different treatment schedules could make different biological effect. The values of biologically equivalent total dose accounted on the base of LQ formula which takes into consideration sublethal damage repair time and cell proliferation time vary from 10.4 Gy to 6.1 Gy for tissues characterized by a/b = 25 Gy and from 18.9 Gy to 6.4 Gy for a/b = 2 Gy. Assuming that radiobiological parameters change during treatment we can also note that biologically equivalent total dose depends on fractionation schedules, but the value may be different from expected. For example, for early reacting tissues total 9 Gy given in 3 fractions could be more effective than single 9 Gy dose (Table 5a).

CONCLUSIONS

From calculations performed it appears that the influence of radiobiological parameters and physical factors of radiation is greater for late than early responding tissues.

Without exact knowledge of radiobiological parameter values used in LQ formula, it is mpossible to state the biological effectivenes of used radiotherapy schedule.