APPLICATION OF TIME-DOSE-FRACTIONATION RELATED TO THE PRACTICAL PURPOSES IN TREATMENT SCEDULING

Setiono Diran, Asmino, Haryogya Sandi, Sugiarto - Suwitodihardjo, Bambang Widjanarko and Bambang Darmanto Seno.-

Deparment of Radiology, Dr. Soetomo Hospital
University of Airlangga, Surabaya, Indonesia.-

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For the last 20 years, we have known the excellent work of Strandqvist, Ellis, Orton, Kirk, Lokajicek etc. In their biological effects. Those have been translated by physicists in terms of mathematical approximation of the dose, fractionation and the overall time of the radiation with the biological effects of ionizing radiation form sublethal injury.

Yet, there are still quite a lot of factors which should be considered in evaluating the biological effects of normal tissues and tumors, such as : cellular variation of different organs, nutritional state, vascularisation, oxygenation of the tissue, volume of treated area and also the quality of radiation, etc.

Orton (20) stated that there are only an approximate representation of a highly complex sequence of biological events that occur during a course of radiation therapy. It is based on clinical evidence, obtained by retrospective analysis of typical radiotherapy data and hence should be used with great caution, if the time dose and fractionation differ significantly from that commonly used in conventional radio-therapeutic practice

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But so far NSD/CRE formula are the best estimators of tissue damage that we have (Wheldon. 15). And we have tried to apply them for practical purposes in planning of the treatment schedule.

Method :

The scheduling of radiation treatment based on several considerations.

1. All patients admitted in the hospital receive a daily radiation therapy, five times a week. Patients who are in a state of good performance receive a daily fractional dose of 200 cGy. The dose can be reduced depend on the condition of the patients, the tolerance and volume of the irradiated area.
2. Patients who are treated ambulatory are mostly in a good general condition. They are able to go to the hospital for their radiation and the radiation arrangement is three times a week. It will give them one day rest after radiation treatment. This mean a lot, especially when the radiation reaction begins to develop. It also has a benefit to increase the number of patients to be treated per week.
3. Patients who come from out of town are given less fractionation, once or twice a week. Those patients should be in a good physical condition as to tolerate a higher fractional dose. They may stay longer with their family and reduce cost of transportation compared with daily radiation. Those who are able to commute, do not need hospitalisation or hotel stay.
4. Patients who come in a late stage of the disease, with local advanced or inoperable disease, but with

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fairly good general condition, treatment will be given with large fractionation dose and with few fractions in order to provide a shock dose to decrease the size of the tumor for palliative purposes.

The next step after designing the fractionation is to calculate the fractional dose as such that the dose-fractionation combination will give similar biological effects as the standard dose-fractionation, 1000 cGy per week in 5 fractions.

For example : to determine the dose for 3 times a week fractionation. We use the ELLIS formula :

$$NSD = D \times N^{-0.24} \times T^{-0.11} \text{ or}$$

$$= d \times n^{0.76} \times T^{-0.11} \text{, in which :}$$

D is total dose, d is fractional dose

For dose-fractionation 1000 cGy/week, 5 times a week :

$NSD = 200 \times 5^{0.76} \times 7^{-0.11}$ rets

and dose-fractionation d cGy/week, 3 times a week :

$NSD = d \times 3^{0.76} \times 7^{-0.11}$ rets.

When we wish to achieve an iso-biological effect of those dose fractionation, then the NSD should be the same : $200 \times 5^{0.76} \times 7^{-0.11} = d \times 3^{0.76} \times 7^{-0.11}$, then d = 295 cGy. So the fractional dose for 3 times a week will be roughly 300 cGy.

The same calculation to be used when we wish to have other fractionation :

Fractions	Fractional dose
Once a week	680 cGy --- 700 cGy
Twice a week	401 cGy --- 400 cGy

...... 3 times a week

3 times a week	295 cGy --- 300 cGy
4 times a week	237 cGy --- 240 cGy
5 times a week	200 cGy (standard dose-fract.)
6 times a week	174 cGy --- 175 cGy
Hyperfractionation :	
twice a day	118 cGy --- 120 cGy
Low fractionation :	
Once every 2 weeks	1151 cGy ---1200 cGy

In view of the practical stand point, the second dose more practical for daily radiation therapy calculation.

For intracavitary or brachytherapy radiation planning, the fractionation of once every 2 weeks or once a week or twice a week, will be more suitable.

The dose fractionation as mentioned above is based on 1000 cGy/week dose-rate. Suppose the total dose is planned for 4000 cGy, then the overall time T will be 4 weeks. But sometime we like to have another planning, not just 1000 cGy/week. Then we have to modify the formula :

$$NSD = d \times N^{0.76} \times T^{-0.11}$$

If fractionation is planned for once or twice or thrice a week, there is a dependency between N and T, e.g When fractionation is planned for 5 times a week, then T = 7/5 F or T = axF , where a is an known constant.

Then : $NSD = d \times N^{0.65} \times a^{-0.11}$

So in this formula there are only 2 unknown factors, i.e: d and N. Suppose the fractional dose of 350 cGy will be given in fractionation of 3 times a week, then a for this fractionation is 2,333 and a for standard

.... fractionation

fractionation (5 times a week) is 1,4.

Consequently a total dose of 4000 cGy standard dose - fractionation will have a similar iso-biological effect of a fraction. N = 9,22 or with a new total aquivalent dose of 3227 cGy. etc.

The overall time for the standard fractionation to complete 4000 cGy will be 4 weeks, but with the new fractionation of 350 cGy 3 times a week, it will become 3 weeks.

When we want to combine NSD from external radiation and NSD from brachytherapy, then we have to convert into TDF, because NSD is not additive. We are not going to elaborate about TDF, CRE and CBE.

Another possible application of NSD formula is in modifying dose-fractionation is cytostatic therapy. Because cytostatics havq a radiomimatic action similar to the effect of ionozing radiation, i.e. there is cell damage fraction and surviving fraction after a certain dose of treatment, followed by a recovery or repair period from sublethal injury. There is an analogy between the effects of radiation and those of cytostatics which are in the tolerable range to the patients. As an example we use CMF protocol formula from Bonnadona :

C (cyclophosphamide): 100mg/m^2/day in 14 days orally
M (methotrexate) : 80mg/m^2/day in twice, IV
F (fluorouracil) : 600mg/m^2/day in twice, IV.
repeated monthly.

When we work with NSD formula to change the dose from once a month into every week application, while still keeping the iso-biological effect, then it comes out :

C : 827 mg/m^2 every week

M : 47 mg/m^2 every week

F : 709 mg/m^2 every week

There are hundreds of cytostatic protocols available, and this is one way to fractionate the dose according for the need and convenience to the patients.

Results and Discussion.

We have known of the existence of Ellis' formula since 1967, yet we do not realize the importance of that equation in the designing of the time-dose-fractionation to maintain the iso-biological effects of radiation routinely. Actually, long before 1967, Coutard in 1930 had developed a system, which changed the continuous protracted radiation into the daily fractionated radiation, which is still used up till now. Strandqvist in 1944 made experimentation with several fractionation and various dasages and plotted in a logarithmic graph and revealed a dose, fractionation and effects of radiation.

We did the same experiment to patients early in 1982 with those dose-fractionation arrangement. It appeared that the side effects of the radiation, wether they were acute or late effects, were not worse than original daily 200 cGy dose. Moreover the tumor control on operable and the non-operable cases were more or less the same with 200 cGy daily fraction. So then we have decided to use that system routinely since 1983.

Below are listed the number of patients that have been given the various dose fraction.

	dose fraction	number of patients	
1984	100 cGy	32	
	150 cGy	454	2%

	175 cGy	--	
	200 cGy	7887	30%
	250 cGy	2	
	300 cGy	17553	68%
	400 cGy	2	
1985	100 cGy	172	0.5%
	150 cGy	451	2%
	175 cGy	--	
	200 cGy	1754	8%
	250 cGy	163	0.5%
	300 cGy	20561	89%
	400 cGy	---	
1986	100 cGy	21	
	150 cGy	123	
	175 cGy	--	
	200 cGy	1528	7%
	250 cGy	552	3%
	300 cGy	18895	90%
	400 cGy	4	

It is obvious, that the radiotherapists in our intitution prefer to use 300 cGy fraction 3 times a week And it also shows that most of the patients prefer to stay in the city, without being hospitalized.

It also is of great interest to discuss here the use of the split-course radiation or as it often called the sandwich-therapy, if for some reasons the radiation therapy is terminated for several days, to be continued again later. Douglas Jones (5) devised an equation for a decay factor or patial tolerance, as follow :

$$N_t = N \left(1 + \left(\frac{T}{T + G}\right)^{0.11} \right).$$

Suppose we use 200 cGy, 5 times a week with a total dose of 4000 cGy without splitting, NSD = 1350,91 rets. When we split it and give the patient a rest period of 2 weeks, then the NSD = 1318,5 rets. The difference is 2,4%. etc.

Physicists have devised so many formula as for the purpose of accuracy and perfection, but as radiotherapists or oncologists we see the patients as a whole with all their problems and their variations of life. Several scientists have made their own comments.

Wheldon (15) : the NSD/CRE formula are probably a first order scalar approximation to more complex multidimensional relationship. The inexact nature of the approximation will no doubt become apparent as more varied patterns of therapy are explored. This potential source of error must be born in mind whenever unconventional schedule is under consideration.

Graffman (2) : The parameters of any model should be regarded as lumped quantities, which, if properly chosen reflect some basic characteristics of the real system. The more complex the models become, the more difficult to estimate are the values of the parameters.

Shirley Hornsey (3) : The response of the primary tumors and of metastasis in lymphnodes was better after treatment regimes with large dosis per fraction and few fraction. These results are consistent with the view, that the radioresistance frequently observed clinically, may be due to a large capacity to repair radiation damage in the melanoma cell.

Conclusion :

- NSD is the best estimator for biological effects of radiation in terms of time-dose-fractionation.
- It is better to keep the formula as simplr as possible for practical purposes.

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