CONCEPT OF BIOLOGICALLY NORMALIZED DOSE-VOLUME HISTOGRAMS FOR 3D RADIATION TREATMENT PLANNING

B. MACIEJEWSKI[1], A. NIEMIERKO[2], A. ZAJUSZ[1], K. SKŁADOWSKI[1]

1.Dept. Radiotherapy, M. Skłodowska-Curie Memorial Institute and Cancer Center, branch Gliwice, Poland 44-100 Gliwice, Wybrzeże A. Krajowej 15; 2.Dept. of Radiation Medicine MHG and Harvard Medical School, Boston, USA.

INTRODUCTION

In radiotherapy, various tumor and normal tissue characteristics affect the treatment prescribed for an individual patient. Physical dose is one of predictors of response which can be accurately measured. However, physical dose distribution is not the only factor which determines biological response of tumors and normal tissues. Radiobiological response to physical dose vary as a function of dose per fraction [Withers et al, 1988; Withers et al, 1983]. Models of biological response of tumor and normal tissues to radiation treatment can be a useful tool for evaluation of 3D dose distributions and optimization of radiation therapy [Goitein, 1987; Goitein and Niemierko, 1988; Niemierko and Goitein, 1991; Niemierko and Goitein].

Inevitable inhomogeneity of the dose distribution causes importance of volume factor and dose-volume histograms (DVH) as a useful tool for treatment planning. While accurate measurement and calculation of physical dose distribution within the treatment volume is always an important step of treatment planning, radiation therapy could ultimately be better served by an additional information received from the DVHs which account for varying tissue sensitivity for change in dose per fraction.

The aim of this paper is to provide a simple method for employing information on variation in tumor and normal tissue sensitivity for change in fractionation parameters to biologically normalized dose-volume histograms (BNDVH) using linear - quadratic formula. The L-Q formula, which is an essential component of this model, is already well known, but the proposed application is new. The BNDVH concept can be used for evaluation of competing dose distributions and do not require time consuming calculation of the entire 3-dimensional dose distribution.

MATERIAL AND METHODS

Despite the recent advances in technology of computers and imaging devices, the conventional 3-dimensional treatment planning is still a very time consuming process. More (valuable) information regarding treated patient (such as CT, MRI or USG images) means more data which has to be extensively processed. Three-dimensional dose calculation is much slower then it is for 2-dimensional cases, not only because there are approximately two orders of magnitude more points to calculate dose at, but also, because good, 3D algorithms take advantage of this extra information about 3D geometry and 3D scatter effects. Computer optimization of 3D dose distribution is still a very time consuming process.

The computational burden associated with 3-dimensional treatment planning can be substantially reduced when one realizes that for evaluation and assessment of treatment plans there is no need to calculate dose within entire volume defined by CT slices. It is sufficient when dose distributions and derived information such as dose-volume histograms, dose statistics and estimates of tumor control probability and normal tissue complication probabilities are calculated over selected volumes of interest [Niemierko and Goitein, 1991; Niemierko and Goitein]. These volumes of interest are target(s), organs at risk and eventually other structures which should be taken into account. As we elaborated elsewhere, calculating of dose at points randomly positioned inside each volume of interest (instead of using rectangular matrix of points) can further reduce the number of calculational points at least tenfold without decreasing accuracy [Niemierko and Goitein, 1990]. For most clinical cases we use 400 randomly positioned points per volume of interest. For unusually large and geometrically complex structures, less points is generated according to formula that the average distance between calculational points do not need to be less then 2mm [Niemierko and Goitein].

The clinical usefulness of dose-volume histograms for 3D treatment planning has been proven [Chen, 1988; Shipley et al, 1979]. In constructing DVH we use an approach we term volume-dose distribution. This is a cumulative distribution whose computed points are equally spaced in the volume rather than dose dimension. It is computed by sorting the calculational points in order of decreasing dose, and then plotting dose

versus point index number multiplied by the average volume per point. Using this approach, no information is lost (regular DVH is constructed by binning points, i.e., information is averaged over a set of points composing an each bin) and it can be used even for a small number of points [Niemierko and Goitein, 1991; Niemierko and Goitein].

Dose-volume histograms are a useful treatment planning tool because dose distributions within volumes of interest are inhomogeneous (if they were homogeneous, one number would completely describe the dose distribution). Biological response of a particular organ depends, however, not only upon details of the dose-volume distribution but also upon the way the dose was delivered i.e. upon the fractionation scheme. Therefore, it seemed to us that a concept of DVH including an extra information regarding tissue sensitivity (through α and β parameters of the linear - quadratic model) and fractionation scheme (through number of fractions or dose per fraction) would be a helpful tool when evaluating various treatment plans.

According to the linear - quadratic model [18] the (cellular) effect of every fraction (partial effect) can be expressed as a product of physical dose **d** and fractionation factor:

$$PE(d,\frac{\alpha}{\beta}) = d(\frac{\alpha}{\beta} + d)$$

- (1)

When total dose D is delivered in N fractions (not necessarily of equal dose) the total effect is a sum of partial effects:

$$TE(\{d_i\},\frac{\alpha}{\beta}) = \sum_{i=1}^{N} PE(d_i,\frac{\alpha}{\beta}) = \sum_{i=1}^{N} d_i(\frac{\alpha}{\beta} + d_i)$$

- (2)

The same effect can be achieved when dose is delivered in equal fractions of 2Gy up to the biologically equivalent, unknown dose BND_2 (which stands for Biologically Normalized Dose):

$$\sum_{i=1}^{N} d_i(\frac{\alpha}{\beta} + d_i) = BND_2(\frac{\alpha}{\beta} + 2)$$

- (3)

Equation (3) is an iso-effect equation which allows calculating physical dose BND delivered in equal fractions of 2Gy, equivalent (in terms of the same fraction of surviving cells) to dose $\sum d_i$ delivered in N fractions of dose d_i each:

$$BND_2(\{d_i\},\frac{\alpha}{\beta}) = \frac{\sum_{i=1}^{N} d_i(\frac{\alpha}{\beta} + d_i)}{\frac{\alpha}{\beta} + 2} = \sum_{i=1}^{N} d_i(1 + \frac{d_i - 2}{\frac{\alpha}{\beta} + 2})$$

- (4)

We normalize dose to equivalent dose delivered in equal fractions of 2Gy but, of course, normalization to a different dose per fraction can be used. We use 2Gy because most published dose-response curves are obtained (or recalculated) for this dose per fraction [Maciejewski, 1991; Maciejewski et al, 1989; Withers et al, 1984].

When all N fractions ale equal (to dose d) the equation (4) reduces to simpler form:

$$BND_2(N \cdot xd,\frac{\alpha}{\beta}) = D(1 + \frac{d - 2}{\frac{\alpha}{\beta} + 2} = DNF(d,\frac{\alpha}{\beta})$$

- (5)

It is obvious from equation (5) that fractionation effects (expressed through normalization factor NF) are larger for tissues and endopoints with smaller α/β ratio and that the absolute effect (i.e. expressed in Gy) of fractionation different than 2 Gy per fraction is linearly proportional to the total dose D. We would like to emphasize that BND is not a biological dose or a measure of biological effect. It is a physical dose expressed in dose units (Gy) which gives the same cell survival fraction as dose D given in egual fractions of 2 Gy.

Equations (4) or (5) can be directly used to recalculate value of every bin of the DVH (i.e. dose at each calculational point in our volume-dose distribution). The resulting product we call Biologically Normalized Dose-Volume Histogram (BNDVH) as it contains not only information about dose-volume distribution but also takes into account sensitivity of irradiated organ (through α/β value) and fractionation scheme (through number of fractions and dose per fraction).

RESULTS

Example 1

To demonstrate the influence of fractionation effects on the BNDVH for tumor and normal tissues we choose the case qualified to the proton therapy at the MGH in Boston. The spinal cord was very close to the tumor and partially within the irradiated volume. The BNDs were calculated for 20, 30, 40 and 50 fractions

regimens using the α/β rations of 15 Gy for tumor and of 2.0 Gy for spinal cord [Maciejewski et al, 1989; Williams et al, 1985].

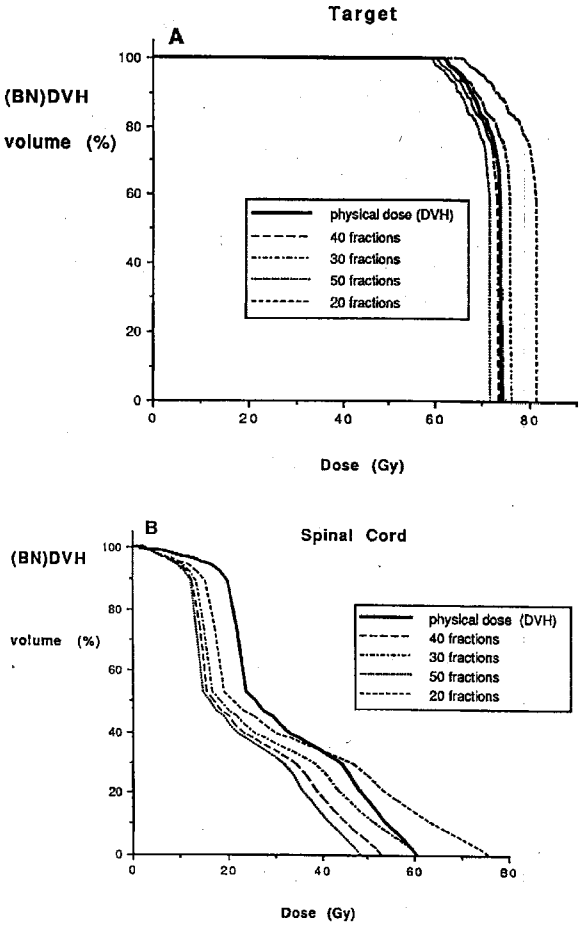


Fig. 1 Physical (solid line) and biologically normalized dose-volume histograms (BNDVH) for 4 fractionation schemes for target (Fig. 1 A) and spinal cord (Fig. 1 B).

BNDVHs for tumor and spinal cord were constructed using expression (5). Figure 1a shows the BNDVH for the tumor and Figure 1b for the spinal cord. For tumor, each value of α/β of above 15 Gy does not greatly modify the BND value (1 - 4% increase in the BND). Figure 1a shows that 100% of tumor volue receives a total dose of at least 60 Gy, regardless of fractionation schedule.

Assuming the TCD90 dose of 66 Gy , this dose is given to about 90% of the tumor volume. Within 10% of the tumor volume, the choice of 20 - 30 fraction regimens would change an effective biological dose of about 10%, whereas if a larger number of fractions is chosen, no more than 5% change in effective biological dose is observed.

For the spinal cord (Figure 1b), BNDVH shows that 20% of the irradiated spinal cord receives more than 50 Gy. If 20 fractions would be given, the BND higher than 50 Gy will be delivered to more than 30% of the irradiated volume. In contrast, for 40 - 50 fraction regimens, 100% of irradiated volume would receive the BND less than 50 Gy.

Example 2

The case of abdominal tumor irradiated with 35 Gy of total dose using large abdominal fields including whole kidney without partial shielding was chosen and the BNDVH for kidney was constructed using an α/β equal to 1.6 Gy [Williams et al, 1985]. Figure 2 shows BNDVHs calculated for the same fractionation regimens as were used for example 1. The BNDVH for physical dose (solid line) shows that 20% of the volume would receive a total dose exceeding 25 Gy. However, when a various fractionation schedules are accounted for, it is seen that 100% of kidney volume receives the equivalent BND smaller than 25 Gy.

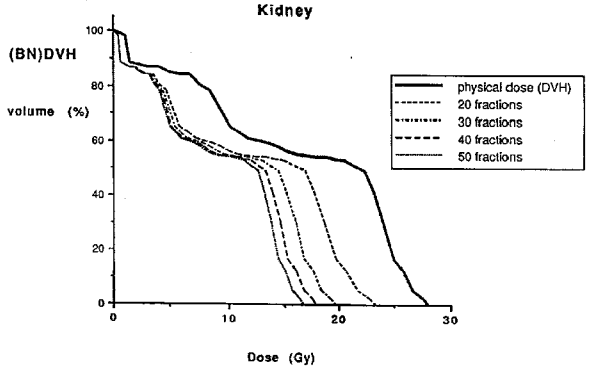


Fig. 2 Physical (solid line) and biologically normalized dose-volume histograms (BNDVH) for 4 fractionation schemes for kidney.

DISCUSSION

The presented method of calculating the biologically normalized dose-volume histograms (BNDVH) is a simple and easy to use in practice. The most important aspect of the proposed method is that BNDVHs are a better tool for a comparsion of various treatment approaches and fractionation schedules than dose distribution display because, even if all fields are treated the same day the isoeffect lines follow the isodose lines only within the same structure (or tissue characterized by the same α/β).

The presented analysis shows, at the first glance, a relatively small of fractionation effects on the shape of the BNDVH for tumor. However, it may depend on the choice of TCD dose level. If 60 Gy would be the prescribed TCD90 then the BNDVH variations shown in the Figure 1 are insignificant for tumor control probability because, 100% of the tumor volume receives that dose. Assuming that 9 logs cell killing is required for local tumor control (p cure = 0.9) and that the

TCD90 is 66 Gy, the dose D10 necessary to reduce the cell survival by 1 logarithm to 10% would be 66/9 = 7.3 Gy and the change in total effective dose of an average of 10% would correspond to one log10 and it would result in a change in local control of about 10 - 15%. Figure 1 shows variations in total dose of about 3.5 Gy - 7 Gy within 20% of tumor volume which may cause a decrease in the probability of local tumor control (Fig. 3) and an increase of the risk of local failure. This example implies that the prediction of local tumor control probability depends on a chosen level of the TCD and biological characteristics of an individual tumor and then, even a small variations in the BNDVH should not be ignored.

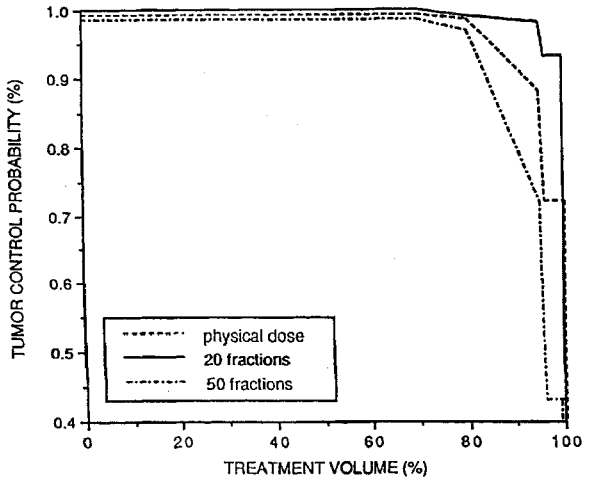


Fig. 3 Tumor control probability versus treatment volume from the BNDVHs in Fig. 1 A assuming TCD 90 = 66Gy and that 9 logs cell killing is required for TCP = 0.9.

Many authors have offered models of complication probability as a function of dose and irradiated volume. Lyman and Lyman and Wolbarst [Lyman,1985; Lyman and Wolbart, 1988] proposed a 3-parameter model where the complication probability is expressed as an error function and a power law describes a dose-volume relationship. The dose response curve for late effect in normal tissue and its steepness varies as a function of volume [Withers et al, 1988] and tolerance can not be viewed or expressed simply as a function of dose. The risk of complications depends on the organization and size of the respective functional subunits - FSU [Withers et al, 1988; Withers et al, 1993]. We have constructed the BNDVHs for two organs, i.e. spinal cord and kidney to compare the effect of different organization of the FSUs in these organs: the spinal cord has a series organization and FSUs in kidney (nephrons) are organized parallelly. In the spinal cord the damage of a single FSU causes a fatal late complication (myelopathy) whereas Glatstein [Glatstein,1973] and Steckel [Steckel et al, 1974] have found, that even heavy damage of 50% of kidney volume does not reveal clinical dysfunction (due to compensatory function of the remaining 50% of kidney).

Risk dose (RD) curves (Fig.4) for spinal cord and kidney estimated from clinical data [Glatstein, 1973; Maciejewski, 1991; Schultheiss, 1990; Withers et al, 1984] by logistic regression [Walker and Suit, 1983] were used to convert the BNDVHs into the risk curves plotted against the irradiated volume of respective critical organs (Fig. 5) .

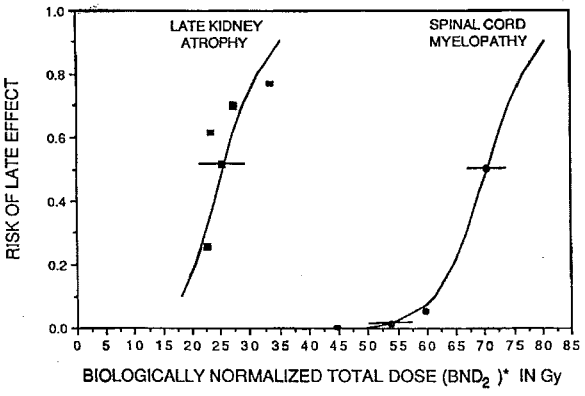
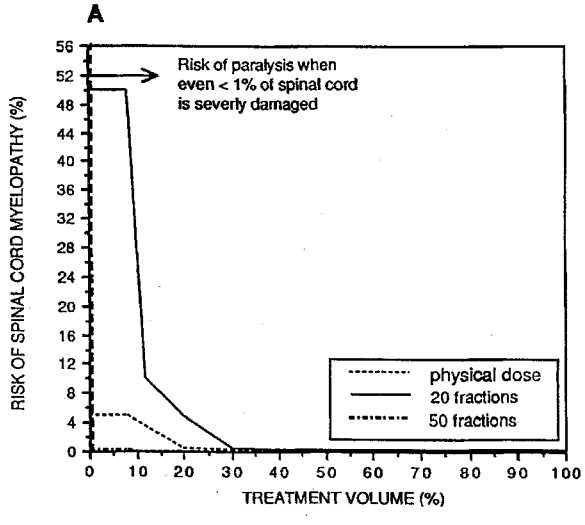


Fig. 4 Risk dose curves for late kidney atrophy and spinal cord myelopathy estimated from clinical data [Glatstein, 1973; Maciejewski, 1991; Schultheiss, 1990; Withers et al, 1983]

Assuming that 50 Gy given in 2 Gy fractions cause 0.2% risk for spinal cord, Figure 5 shows that 20 fraction regimen is unacceptable because of a high risk of late myelopathy. Among the tested fractionation regimens, only 50 fractions can be considered as a low risk treatment.



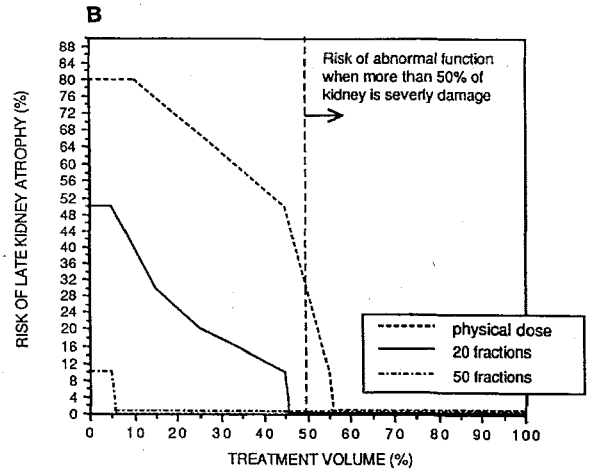


Fig. 5 Late effect risk curves for (A) spinal cord and (B) kidney plotted against the irradiated volume of respective organs. Risk cirves were estimated using risk doses from Figure 4.

While from the clinical point of view even 1% risk for spinal cord damage is unacceptable, for kidney, severe damage of the 50% of its volume may functionally be compensated by the remaining undamaged volume of this organ. Figure 5 shows for kidney that risk probability curves for each of the analyzed fractionation regimens give a tolerable risk of a functional failure of the kidney .

Presented examples illustrate how the BNDVH can be interpreted to choose the optimal physical dose distribution and the best fractionation scheme. The BNDVHs may provide an important information for optimization of radiation treatment planning especially with regards to the estimation of the risk of late effect for normal tissues. It should be emphasized that BNDVHs can be calculated and treatment plan can be evaluated before the complete 3D dose distribution is calculated. It is sufficient when dose is calculated at a certain, relatively small number of points generated only within the regions of interest.

REFERENCES

1. Chen, G. T. Y. Dose volume histograms in treatment planning. Int. J. Radiat. Onkol. Biol. Phys. 14: 1319-1320, 1988.
2. Glatstein, E. Alterations in rubidium-86 extraction in normal mouse tissue after irradiation. An estimate of long - term blood flow changes in kidney, lung, liver, skin and muscle. Radiat. Res. 83: 88-101, 1973
3. Goitein, M. The probability of controlling an inhomogeneously irradiated tumor. In: „ Report of the working groups on the Evaluation of Treatment Planning for Particle Beam Radiotherapy" prepared under contract for National Cancer Institute, September 987.
4. Goitein, M. Niemierko, A. Biologically based models for scoring treatment plans. in Proceedings of the Joint U.S./Scandinavian Symposium on Future Directions of Computer - Aided Radiotherapy. San Antonio, Texas, pp. 1-22, 1988.
5. Lyman, J.T. Complication probability as assessed from dose-volume histograms. Radiat. Res. 104, suppl.pp. 13-19,1985
6. Lyman J.T. Wolbart , A.B. Optimization of radiation therapy. Part III. A method of assessing complication probability from dose-volume histograms. Int. J. Radiat. Oncol. Biol. Phys. 14: 103-109, 1988.
7. Maciejewski B. Biologiczne dawki ryzyka -IZOBIOgy-2. w „Tolerancja zdrowych tkanek w radioterapii. Odczyny popromienne" wyd. Centrum Onkologii, Gliwice, 1991, pp. 159 - 175.
8. Maciejewski B., Withers, H. R., Taylor J. M. G. Hliniak A. Dose fractionation andregeneration in radiotherapy for cancer of the oral cavity and oropharynx. Tumor dose-response and repopulation. Int. J. Radiat. Oncol. Biol. Phys. 16: 831-843, 1989.
9. Niemierko A., Goitein M. Random samplingfor evaluating treatment plans. Medical Physics 17: 753 - 762, 1990.
10. Niemierko A., Goitein M., Calculation of normal tissue complication probability and dose-volume histogram reduction schemes for tissues with critical element architecture. (in press) Radiother. Oncol. 1991
11. Niemierko A., Goitein M., UrieM. Optimization of 3D radiation therapy with both physical and biological end points and constraints. accepted for publication in Int. J. Radiat. Oncol. Biol. Phys.
12. Schultheiss T. E. Spinal cord radiation tolerance: doctrine versus data. Int. J. Radiat. Oncol. Biol. Phys. 19: 219- 221,1990.
13. Shipley W. U., Tepper J. E., Prout G. R., Verhey L.J., Mendiondo O. A., Goitein M., Koehler A. M., Suit H. D., Proton Radiation therapy in patients with localized prostatic carcenoma. JAMA, 241: 912 - 1915, 1979.
14. Steckel R. J., Collins J. D., Snow H. D., Lagasse L. D., Barenfus M., Anderson D. P., Wiesenburger T., Huskins L. A., Ross N. A., Radiation protection of the normal kidney by selective arterial infusion. Cancer 34: 1046 - 1058, 1974.
15. Walker A. M., Suit H. D., Assessment of local tumor control using censored tumor response data. Int. J. Radiat. Oncol. Biol. Phys. 9: 383 - 386, 1983.
16. Williams M. V., Denecamp J., Fowler J., 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.
17. Withers H. R., Taylor J. M. G., Maciejewski B., Treatment volume and tissue tolerance. Int. J. Radiat. Oncol. Biol. Phys. 14: 751 - 759, 1988.
18. Withers H. R., Thames H. D., Peters L. J., A new isoeffect curve for change in dose per farction Radiother. Oncol. 2: 173 - 174, 1984.
19. Withers, H.R., Thames H. D., Peters L. J., Fletcher G. H., Normal tissue radioresistance in clinical radiotherapy. in G. H. Fletcher, C. Nervi and H. R. Withers (eds.) Biological bases and clinical mplications of tumor radioresistance. Masson Publ. USA, Inc. pp. 139 - 152, 1983.