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Complication Probability as Assessed from Dose–Volume Histograms

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Optimization of a treatment plan for radiation therapy will produce a plan with the highest probability for tumor control without exceeding an acceptable complication rate. To achieve this goal it is necessary to have a means to estimate probabilities of local control and normal tissue complication. In general, good treatment plans deliver a high uniform dose to the target volume and lower doses to the surrounding normal tissues. The tolerance dose values available for various normal tissues are usually assumed to apply to partial or full volumes of the tissue which have been uniformly irradiated. These values are the best guidelines for estimating complication probabilities in tissues that receive a uniform dose to a fraction of the tissue and no dose to the remainder. Dose–volume histograms are one means of evaluating the uniformity of the irradiation on the tissues. Frequently the normal tissues are not uniformly irradiated as is demonstrated by dose–volume histograms for different treatment plans. A recursive algorithm which uses these tolerance dose data has been written and can be applied to arbitrary dose–volume histograms to estimate the complication probability.

INTRODUCTION

Treatment planning optimization involves selection of an acceptable plan that controls the local and regional spread of cancer without causing normal tissue complications (*1*). To fully optimize a treatment plan (maximize the tumor dose without exceeding an acceptable complication probability), a method is needed to determine the complication probabilities for the different normal tissues which will be affected by the treatment.

Sophisticated treatment planning, particularly for particle beam therapy, involves three-dimensional calculations or a series of two-dimensional calculations using adjacent slices of CT data (*2*). To evaluate a given plan, the radiotherapist must integrate the information presented by series of isodose distributions superimposed on the CT images. All the slices, which demonstrate the target volume and the critical tissues, must be examined to ascertain that the target is adequately treated and the normal tissues are adequately spared. Heavy charged-particle beams offer a means for sparing normal tissues from irradiation that is not available with conventional radiations. Decisions to maximally spare normal structures must be tempered by the possibility of not adequately treating normal tissues bearing occult disease.

If dose–volume histograms are calculated from the data presented in the isodose distributions, the degree of uniformity or nonuniformity of the irradiation may be

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quickly assessed because a single histogram can present dose uniformity information which is contained in a number of sets of isodose distributions (*3*).[1,2] The histograms give another way to look at the plan and may give some additional information that is not readily apparent when using the isodose distributions. A high-dose region in the histogram may represent a high-dose region that is related to a single CT slice or may represent a contiguous region related to adjacent CT slices or even a number of isolated high-dose regions related to the same or different slices. The isodose distributions are needed to determine the location of the high-dose regions. Therefore the dose–volume histograms do not substitute for the isodose distributions in the evaluation of a treatment plan, but augment them.

The purpose of this study is to develop a method to estimate the complication probability of a normal tissue structure from a dose–volume histogram and data from a population of radiation therapy patients. The estimates of the complication probability can then be used to optimize a treatment plan. The identification of the optimal plan is also subject to clinical judgment of the acceptability of the plan and the risk/benefit for each individual patient. This approach is being explored in the optimization of heavy-charged-particle treatment plans. An evaluation of several representative cases has led to some generalized conclusions which may provide guidance to the radiotherapist in assessing appropriate treatment plans. The techniques developed in this work are equally applicable to optimization of treatment plans for other radiations.

METHODS

Data from the literature which might aid in this ranking are values of the tolerance dose of various tissues (*4–6*). Tolerance doses are usually given as a function of beam area, or length of the irradiated portion of structure, or fraction of the organ treated. These data, which are part of the folklore of radiotherapy, are for treatment with low-LET radiations and a conventional fraction schedule. These values were derived from observation of patients who were treated before the days of sophisticated treatment planning. Therefore it must be assumed that there could be significant errors in the estimation of the portion of the organ or tissue which received the irradiation and in the uniformity of the irradiation. These data, which are the best available, are not as complete or as firm as desirable.

The best example of the tolerance dose (in Gy) is for the heart (Table I). The data for the partial-volume irradiations are from Rubin *et al.* (*5*), while the remaining point represents the collective judgment of several experienced therapists who are participating in an NCI-sponsored project to evaluate particle treatment plans. The TD_{50} and TD_5 are the doses that would result in 50 and 5% complication probabilities after 5 years, respectively, and represent two points on what is assumed to be a sigmoid-shaped dose–response curve. These data imply that the complication probability is a function of both the percentage volume irradiated and the absorbed dose received by the volume. There are many other factors that are involved, most noticeably the fractionation scheme; however, for the moment this and all these other factors will be held constant.

Data for other partial volumes and tolerance levels can be obtained by interpolation or extrapolation. A full set of data can be represented by a three-dimensional surface that represents the probability of complication as a function of both the volume and the dose (Fig. 1). This surface was determined by assuming that the volume dependence could be represented by a power-law relationship (*7, 8*).

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[1] S. R. Zink, J. R. Castro, G. T. Y. Chen, J. M. Collier, J. T. Lyman, and W. M. Saunders, Treatment planning study compares heavy ion radiotherapy with photons for carcinoma of the esophagus. Manuscript submitted to *Int. J. Radiat. Oncol. Biol. Phys.*

[2] M. M. Austin-Seymour, G. T. Y. Chen, J. R. Castro, W. M. Saunders, S. Pitluck, K. H. Woodruff, and M. Kessler, Dose volume histogram analysis of liver radiation tolerance. Manuscript submitted to *Int. J. Radiat. Oncol. Biol. Phys.*

TABLE I

Tolerance Doses for Heart

% *Volume*	TD_{50}	TD_5
25	80	70
60	55	45
100		35

$$TD(V) = TD(1)/V^n, \tag{1}$$

where $TD(V)$ is the tolerance dose for a given partial volume (V), $TD(1)$ is the tolerance dose for the full volume, and n is a fitted parameter. The dose dependence is represented by the integral of a normal distribution (one of several possible representations of a sigmoid curve).

$$P_c = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-t^2/2} dt, \tag{2}$$

where $t = (D - TD_{50}(V))/\sigma(V))$. This curve is completely defined by the mean ($TD_{50}(V)$) and the standard deviation ($\sigma(V)$) which for the current work has been approximated by $m \times TD_{50}(V)$. The three-dimensional surface can then be completely defined by the three parameters, $TD_{50}(1)$, n, and m.

Table II is an example of partial-volume tolerance doses for the heart (in Gy) calculated with Eqs. (1) and (2) and parameters derived from the data in Table I. Calculated values for points that correspond to values in Table I are underlined. Values of $TD_{50}(1)$, n, and m for a selected list of organs and tissues are given in Table III. These values are preliminary estimates based on published and unpublished data and opinions; as such, they should be used with caution. It is anticipated that better parameters will emerge from studies using three-dimensional treatment planning systems and dose–volume histograms.

Cumulative dose–volume histograms for a kidney for several possible treatment plans are shown in Fig. 2. These histograms show the fraction of the organ which receives a dose equal to or greater than a given value. The histograms were derived from treatment plans using helium, carbon, or neon beams with field arrangements of two, three, or four fields. For the two-field arrangements all beams produced essentially the same histogram, the one with the largest dose. The four-field arrangement gives the lowest doses with helium being lower than carbon which is lower than neon. This same ranking occurs with the three-field arrangements. It is not difficult to determine the most desirable distribution and even the relative ranking of these histograms by visual inspection. The average dose or the integral dose can also be used to aid in the rankings. However, these methods do not provide an estimate of the clinical significance of the differences between the histograms. Provided there are sufficient data to obtain an estimate of the three-dimensional complication surface, an estimate of the probability for complication can also be obtained, since these histograms represent a fairly

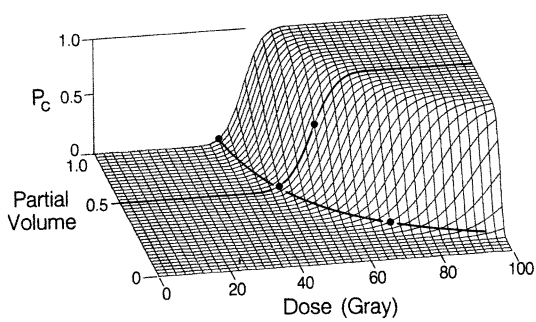

FIG. 1. A three-dimensional surface representation of the probability of complication for the heart as a function of the dose and the partial volume which is uniformily irradiated.

TABLE II
Derived Tolerance Doses for Heart

V	$TD_{50}(V)$	$TD_5(V)$
0.200	93.7	78.3
0.250	83.8	70.0
0.300	76.5	63.9
0.350	70.8	59.2
0.400	66.2	55.4
0.450	62.5	52.2
0.500	59.5	49.5
0.550	56.5	47.2
0.600	54.1	45.2
0.650	52.0	43.4
0.700	50.1	41.8
0.750	48.4	40.4
0.800	46.9	39.1
0.850	45.5	38.0
0.900	44.2	36.9
0.950	43.0	35.9
1.000	41.9	35.0

uniform partial-volume irradiation. The differences between the estimates of the probability of complication give a measure of the clinically important differences between the histograms. Incidentally, with a target dose of 66 Gy, only the histogram representing the two-field arrangements will yield a clinically significant probability of complication. In general, the comparison of the dose–volume histograms of the same organ

TABLE III
Factors for Deriving Tolerance Doses

Organ/tissue	TD_{50}	n	m
Bladder	72.0	0.10	0.1
Bone	70.0	0.05	0.1
Brain	64.0	0.20	0.1
Brainstem	64.0	0.05	0.1
Cauda equina	57.5	0.10	0.1
Esophagus	66.0	0.15	0.1
Eye	60.0	0.05	0.1
Femoral head	62.0	0.05	0.1
Heart	41.9	0.50	0.1
Intestine	55.0	0.10	0.1
Kidney	29.0	0.15	0.1
Liver	35.0	0.40	0.1
Lung	22.0	0.65	0.1
Mandible	77.0	0.05	0.1
Optic nerve	65.0	0.05	0.1
Parotid	72.0	0.10	0.1
Pituitary	54.0	0.05	0.1
Rectum	75.0	0.10	0.1
Spinal cord	50.0	0.10	0.1
Stomach	55.0	0.35	0.1

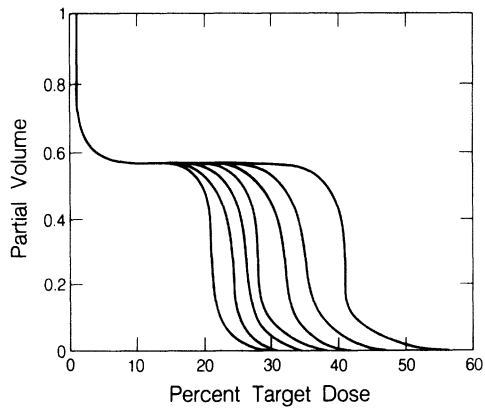

FIG. 2. Cumulative dose-volume histograms for the incidental irradiation of a kidney. Differences are related to the number of treatment fields and the type of radiation employed.

of two rival plans may not be as simple as these initial considerations may suggest because the two distributions may have dissimilar shapes (Fig. 3). The difference between these histograms is that one histogram represents a treatment plan that takes a small volume to a higher dose while minimizing the dose to a larger volume while the other plan does the converse. The clinical significance of the dose distributions represented by these histograms depends upon the type of tissue. Some tissues will be more tolerant of small-volume high-dose regions than others. To estimate complication probabilities for the general case (one which cannot be approximated by a single-step histogram), a recursive histogram-reduction algorithm has been developed.[3] The algorithm is used to determine an estimate of the complication probability from the two highest dose steps of the histogram, and then the algorithm is recursively used to sum the partial contributions from the remaining steps of the histogram. The measure of the complication used for the histogram reduction is the standardized normal deviate, which is the number of standard deviations between the mean ($TD_{50}(V)$) and the dose for the dose-volume step in question ($t = (D(V) - TD_{50}(V))/\sigma(V)$). Implicit in this procedure is the assumption that all regions of an organ, represented in a single histogram, have the same radiosensitivity, and no portion of the organ is more critical than another for normal function.[2] Regions of tissues or organs with different radiosensitivities can be handled in separate histograms with different tolerance parameters (*8*).

When there is more than one normal structure at risk for a severe complication, the estimates of the complications can be combined to determine the probability for any complication (*9*).

$$P_c = 1 - \prod_{j=1}^{N} (1 - P_c(j)) . \tag{3}$$

Failure to control the tumor can also be considered as a treatment complication. A probability of tumor-control algorithm (*10*), which uses the dose-volume histogram for the target volume, has been implemented. By combining the probabilities for being complication free, $P_{cf} = 1 - P_c$, and the probability for local control, P_{lc}, it is possible to estimate the probability of complication-free, local control, $P_{cf,lc}$ (*11*). This probability is then used to obtain an optimized treatment plan.

RESULTS

There are some important deductions that can be made from the estimates of the complication probability as represented by Eqs. (1) and (2). If the treatment plan is

[3] J. T. Lyman and A. B. Wolbarst, A general method of assessing complications from dose-volume histograms. Manuscript submitted for publication.

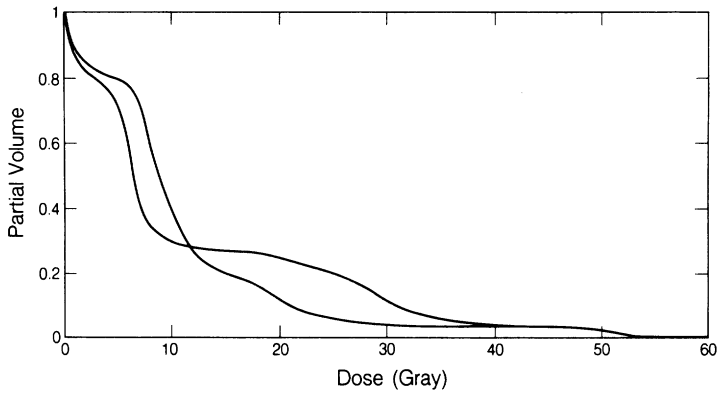

FIG. 3. Cumulative dose–volume histograms for the incidental irradiation of a kidney. These are more complex histograms than those of Fig. 2 and the better distribution is not obvious. Estimates of the complication probability can aid in the selection of the better plan.

designed to have a 5% complication probability, then an error which would result in a 5% overdose will double the complication probability. Similarly, if the tolerance dose is 5% lower than expected the complication probability will also be doubled. Errors in the estimation of the tolerance dose can result from the estimation of the volume irradiated. Assuming 50% of the heart was irradiated when it was really 60% will result in a 10% error in the tolerance dose (Table II). Factors such as fractionation scheme or adjuvant chemotherapy can also result in changes to the tolerance dose. The algorithm used to determine the tolerance doses includes corrections for fraction sizes other than 2 Gy (*12*).

The histogram-reduction algorithm gives the expected result for simple histograms (Fig. 2). The expected result is the estimate calculated by Eqs. (1) and (2) when the histogram is approximated by a single step. For the more general histograms (Fig. 3), where there are no known tolerance dose data, there are no data for comparison. The estimates in these cases appear reasonable when one considers the dose–volume dependence of the tissue (Table III).

DISCUSSION

Individual variations in size and location of tumors can result in higher or lower estimates of complications. If these individual variations are taken into consideration during the treatment planning process, better (lower likelihood of complications) plans may result. This can be considered to be a predictive assay based on patient anatomy and the treatment plan. The result is the identification of the combination of patient and treatment plan which have high or low likelihood for complications. This may result in deviating from standard protocols by using a lower tumor dose for some patients and a higher dose for other patients with similar type tumors.

This approach to optimization of treatment plans is being tested in an NCI-supported project on the evaluation of particle treatment plans. The estimates of the complication probabilities are also being compared with the clinical observations following heavy-

charged-particle irradiations.[1,2] These comparisons will be helpful in establishing the validity of the histogram-reduction algorithm and the data in Table III.

While there are a number of factors that contribute to the probability of complication, it is well established that dose, volume, and fractionation are important factors. Since the complication probability can be very sensitive to the dose and the tolerance dose, accurate estimates of the dose–volume distributions within organs and tissues are needed. This necessitates treatment planning the entire volume containing the structures of interest. From the dose–volume histograms and the tolerance doses, it is a simple procedure to estimate the complication probabilities. These estimates can be used to optimize treatment plans. Treatment plans are not optimized unless they have taken into account the individual variations in size, shape, and location of the normal critical structures relative to the target volume. Comparisons of the observed and the expected complication probabilities would result in better predictions of the complications arising from the nonuniform irradiation of the normal tissues.

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