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Physical and biological aspects of modern radiation therapy planning

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Over the last 20 years radiation oncology has been exposed to exciting biological and technical developments that have a potential to significantly improve the outcomes of cancer treatment. These developments present new opportunities but also create new challenges for the practitioners of radiation oncology. New tools, methods and techniques are required to fully utilize these developments to create, evaluate and optimize the process of radiation treatment. Here a number of tools for planning modern radiation therapy are presented and discussed. In particular, the need for biological considerations in the treatment planning process is emphasized and a concept of Equivalent Uniform Dose (EUD) based on modeling of cell survival and tissue architecture is described. Examples of IMRT dose distributions for a head and neck cancer developed using purely dosimetric (that is, dose and dose-volume) considerations and using EUD-based considerations are shown.

Nowoczesna radioterapia – wpływ osiągnięć w dziedzinie fizyki i biologii na planowanie leczenia

W ciągu ostatnich 20 lat radioterapia onkologiczna uległa znacznemu rozwojowi dzięki fascynującym osiągnięciom, tak w dziedzinie biologii, jak i w zakresie rozwiązań technicznych. Zmiany te mogą znacząco przyczynić się do poprawy wyników leczenia chorób nowotworowych. Niemniej wszelkie zmiany nie tylko stwarzają nowe możliwości, ale stanowią same w sobie wyzwanie. Aby w pełni wykorzystać nowości, potrzebny jest udoskonalony sprzęt, nowe metody i techniki postępowania – tylko wtedy będzie można utworzyć, ocenić i zoptymalizować nowe formy radioterapii. W pracy przedstawiono i omówiono nowe możliwości w zakresie planowania leczenia, a w szczególności potrzebę uwzględnienia uwarunkowań biologicznych w procesie planowania leczenia. Omówiono również ideę Jednolitej Dawki Ekwiwalentnej (Equivalent Uniform Dose – EUD), która powstała w oparciu o modelowanie przeżycia komórek i struktur tkankowych. Przedstawiono również przykłady dystrybucji dawek przy zastosowaniu metody modulowania dawki (Intensity Modulated Radiation Therapy – IMRT) w leczeniu nowotworów głowy i szyi, która powstała w oparciu o uwarunkowania wyłącznie dozymetryczne (dawka i dawka/objętość), z uwzględnieniem Jednolitych Dawek Ekwiwalentnych (EUD).

Key word: radiotherapy, treatment planning, conformal, IMRT, modeling
Słowa kluczowe: radioterapia, planowanie leczenia, IMRT, modelowanie

Introduction

Over the last 20 years radiation oncology has been exposed to a multitude of exciting biological and technical developments that have a potential to significantly improve the outcomes of cancer treatment. On the one hand our understanding of various aspects of cancer biology has been greatly improved by spectacular discoveries in molecular biology and genomics. On the other hand the progress in technology dramatically improved the quality and utility of imaging tumor and normal tissues and the methods of delivery sophisticated treatments. A good example of the former is a new field of Molecular Imaging. For example, Positron Emission Tomography (PET) allows imaging of the metabolic activity of tumor cells and the volumetric distribution of clonogens. Examples of the latter are the Multi-Leaf Collimator (MLC) and Intensity Modulated Radiation Therapy (IMRT) that allow "sculpting" of dose distribution to conform to the target volume while sparing as much as possible the surrounding critical normal structures. These new developments and tools available to practitioners of radiation oncology can greatly benefit the patients but they also present new challenges. It is probably an accurate statement that the progress in technologies related to cancer care has been faster than our comprehensive understanding of the consequences of using these technologies. For example, these days radiation oncologists involved in the state-of-the-art radiation therapy can be faced with complex computer

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"optimized" and "individualized" treatment plans that are very different from the conventional treatment plans, and for which there is none or very limited experience. As is the case with all new technologies there is a great expectation of progress but prudence and critical assessment should be also exercised because on the receiving end of this process are patients under our care.

Here I will discuss only one but important aspect of modern radiation oncology, namely, the methods and tools to assess, compare, and evaluate radiation treatment plans. A radiation treatment plan is a multidimensional object. This is rather obvious considering that patient's anatomy is three-dimensional (3D) and that the treatment agent, namely radiation dose, is not only distributed in a highly non-uniform fashion within the 3D anatomy but also it is distributed in time. Before the 3D era in radiation oncology a description of radiation treatment was, by necessity, rather simple. For example, one could say that the patient received 60 Gy in 30 fractions of 2 Gy per fraction. These days such simple descriptions should be considered inadequate. Any image-based 3D computer radiotherapy planning system provides volumetric information about all important irradiated structures of interest. From viewing 3D dose distributions superimposed onto 3D anatomical structures one can easily appreciate the fact that the actual dose distributions are never uniform, especially for normal structures, therefore cannot be adequately described by a single number. The volumetric and temporal dose inhomogeneity creates problems for reporting, evaluating and comparing rival dose distribution. On the one hand 3D objects cannot be directly compared and ranked without assigning a single number to describe each object. On the other hand, treatment outcomes depend on several biological and dosimetric parameters in a complex manner that despite significant advances in radiobiology is still rather poorly understood.

To better appreciate the type of treatment planning tools that are needed to evaluate the quality of a given radiation treatment plan it is essential to spell out the goals and desired outcomes of radiation therapy. Then, it follows that the ultimate goal of radiation therapy planning is to create a dose distribution that maximizes the likelihood of a desired outcome of radiation therapy. In radical radiotherapy the desired outcome is eradication of the tumor while sparing healthy normal organs and tissues. It follows then that a dose distribution can be judged "good" only when the resulting clinical outcome of radiation therapy is "good." Hence, it seems obvious that the clinical value of a planned dose distribution cannot be evaluated without at least some quantitative consideration of the clinical consequences of dose and dose-volume effects. But how difficult it is to define "good" or, better yet, "optimal" dose distribution? For example, the IMRT requires algorithm-based computer optimization. That is, it requires specifying the goals of radiation treatment in terms understandable to the optimization algorithm. This task is more difficult than it seems. The physicists or dosimetrists designing treatment plans generally assume that the dose prescription provided by radiation oncologist (or by a treatment protocol) represents a complete set of aims of the optimization as well as the reference point for plan evaluation. Although such a comfortable assumption seems obvious and understandable it is important to recognize the associated problems. First, the dose and dose-volume prescriptions are never complete. This is particularly evident in IMRT where there are many more degrees of freedom than in the conventional radiotherapy, and where there are countless significantly different dose distributions that all satisfy the limited set of dose and dose-volume constraints. These different dose distributions may correspond to significantly different clinical outcomes. Second, the clinicians are first to admit that the prescribed dose levels that they use for plan specification and to characterize dose and dose-volume effects in tumors and normal tissues are often appreciably uncertain, particularly when used in novel settings such as IMRT. On the other hand, the physicists and, especially, the computer optimization programs tend to consider those dose and dose-volume constraints as infinitely precise. Third, even when dose and dose-volume constraints entirely describe the desired dose distribution they are often not completely satisfied by the optimized plan. In that case it is important how the deviations from the prescription are evaluated and penalized and how they are weighted against each other. Fourth, there is an obvious antagonistic relationship between an optimal strategy for tumors (higher dose is better, cold spots are bad) and an optimal strategy for normal tissues (lower dose is better, hot spots are bad). The optimal balance between the tumor and the critical normal organs is a complex issue involving biological considerations and clinical judgment. The optimal relative weighting of various normal critical structures is not predetermined but it depends on the structures involved and the magnitude of the departure from the prescription. Clearly, in all non-trivial cases, regardless of the planning approach (either so-called inverse or so-called forward) the optimization and planning process are iterative and require clinically relevant plan evaluation tools and critical judgment.

Materials and methods

Since the discovery of radioactivity and X-rays the practitioners of radiation oncology have been involved in measuring, estimating, and calculating dose. Therefore, the physical dose has been the primary parameter that describes the extent or the magnitude of treatment that a patient receives. Qualitatively the relationship between dose and the resultant effect is fairly simple – more dose corresponds to more tissue damage for both tumors and normal organs and tissues. Therefore, dose-based treatment planning tools have been extensively used in 2D, 3D as well as in IMRT treatment planning. In modern treatment planning environment these tools include various simple dose statistics such as the minimum, the maximum, the mean/median dose for any Volume of Interest (VOI), or say, dose to 95% of the target volume. A convenient tool to summarize and visualize a volumetric characteristic of a dose distribution is Dose-Volume Histogram (DVH) that displays a percentage of the VOI receiving a certain dose [1, 2]. Although the spatial information

is lost when a 3D dose distribution is reduced to a 2D graph, the DVH concept has been effectively used to quickly compare rival dose distributions and represents a standard tool in all 3D treatment planning systems [3-5].

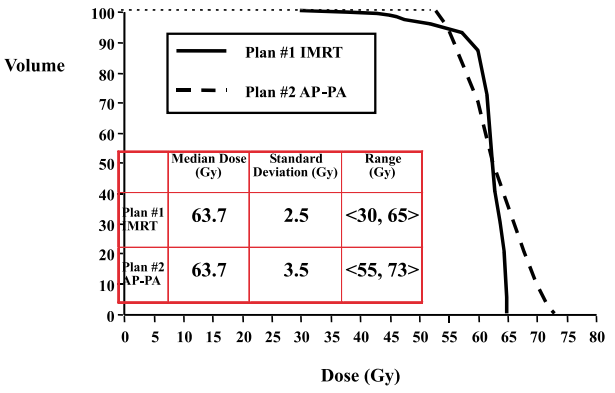

Figure 1. An example of dose-volume histograms for a target volume for IMRT dose delivery (Plan #1 – solid line) and for standard two parallel-opposed fields (Plan #2 – dashed line). A table shows the corresponding standard deviations of the target dose and the range of doses within the target volume.

The dose-based tools are time-honored and practitioners of radiotherapy are quite comfortable using them not only to evaluate treatment plans but also to design treatment plans by explicitly expressing treatment goals in terms of dose and dose-volume requirements and constraints. However, sooner or later one discovers that relying exclusively on dose and dose-volume-based considerations is not sufficient even in apparently simple situations. Figure 1 shows an example. Here, there are two target volume DVHs. One was obtained using two parallel-opposed (AP-PA) open fields and the other one represents an optimized IMRT plan. Both dose distributions are normalized to the same mean dose in the target volume (represented by the DVHs in Figure 1). The IMRT plan was derived using a sophisticated optimization algorithm with the score function designed to minimize the target dose inhomogeneity by minimizing the sum of squared deviations from the prescribed (mean) dose. Nothing was optimized for the AP-PA plan and both field weights are equal. The corresponding DVHs intersect twice. There are two interesting and important questions; 1) which target dose distribution is more uniform? 2) which target dose distribution is better? It is clear that even the simpler first question has no satisfactory answer because the answer depends on our definition of dose uniformity. There are at least two equally reasonable definitions. The first one says that a dose distribution is more uniform if the corresponding standard deviation of dose is lower. According to this definition the IMRT DVH corresponds to a more uniform dose distribution (2.5 Gy versus 3.5 Gy). This is not surprising since the IMRT plan was derived by effectively minimizing the standard deviation of dose. However, equally reasonable measure of dose uniformity is the range of doses. According to this definition the AP-PA dose distribution is more uniform (a range of 28 Gy versus 35 Gy). It is also clear that answering the second question is more complicated and, in fact, it is beyond the scope of purely dosimetric considerations, namely, for the reason that dose is only a surrogate (although, often, a very good one) of clinical and biological considerations. In fact, it is easy to define a criterion by which one can tell which dose distribution is better. It is the one that provides a higher chance of eradicating all the clonogens. In other words, to tell which target dose distribution is better one needs a tool that estimates the Tumor Control Probability (TCP). A similar situation presents for normal structures. A normal tissue dose distribution is better if the corresponding Normal Tissue Complication Probability (NTCP) is lower.

There are several models of TCP and NTCP [6-22]. Most of these models are mechanistic in a sense that they try to model the presumed mechanism of tissue damage by modeling cell kill statistics and tissue architecture. The former is often modeled using the Linear-Quadratic (LQ) model that assumes that the frequency of biologically relevant effects of radiation, E, as a function of dose, D, can be expressed by a quadratic function, $E=\alpha D + \beta D^2$, where α and β are model parameters [23-25]. The latter is often modeled using the concept of Functional Subunit (FSU) and the manner, parallel or serial, that these FSUs are arranged in a tissue or organ [26]. Some models are phenomenological in a sense that they use convenient mathematical formulae to describe the dependence of the probability of outcome of interest (i.e., TCP, NTCP) on the dose, volume, and time parameters without interpreting these formulae in any mechanistic sense, and without interpreting the model parameters in terms of realistic biological entities [11, 27]. Both types of models have been used in various investigations but their clinical use has been limited due to the problems with clinical validation of these models. In order to validate a model one needs a good quality data set or, better yet, several sets that allow estimation of the model parameters with reasonable accuracy and formal testing of the consistency of the model with the data [28]. Additionally, the biological mechanism of tissue response to radiation is very complex and not fully understood, and even the mechanistic biological models are incomplete and describe only what is assumed to be the most important effects. Despite the mentioned problems the models of TCP and NTCP have been shown to be useful for plan evaluation and optimization particularly for IMRT where a vast space of possible treatment plans requires computers to search for the best option [29]. This is possible because for plan optimization one needs to compare only the relative merits of rival plans and ranking of plans using these models can be fairly robust.

The purely dosimetric treatment planning tools are relatively simple, well understood, and can be effectively used in a variety of situations. However, as mentioned above, they represent only surrogates of clinically relevant characteristics of a treatment plan. On the other hand models of tissue response to radiation have potential to describe the actual clinical and biological consequences of any radiation treatment but they try to model mechanisms that are not fully understood and their parameters are rather uncertain due to the weaknesses and incompleteness of the relevant clinical data. To fill the gap between the two approaches we developed a concept of Equivalent Uniform Dose (EUD) [30]. The concept of EUD assumes that any two dose distributions are equivalent if they cause the same specified clinical or radiobiological effect. The clinically relevant effects vary from one normal tissue/organ to another and from tumors to normal tissues. Below we describe the cell-survival-based models for tumors and for normal tissues.

For tumors it is generally accepted that to locally control a tumor all clonogens need to be killed. Therefore, the probability of local control as a function of dose depends on the expected number of surviving clonogens. Assuming that each voxel (sub-volume) of the tumor responds to radiation independently the probability of controlling all (say, N) voxels, P, is the product of the probabilities taken over all voxels of the target volume:

$$P=\prod_{i=1}^{N} P(D_i),$$

where D_i is the dose at the i'th voxel and $P(D_i)$ is the probability that all clonogens within the i'th voxel are killed. For doses typically used in curative radiation therapy the probability of survival for a single clonogen is very small and the number of clonogens is relatively large. Therefore, the Poisson statistics of

events can be applied and the probabilities $P(D_i)$ can be modeled as

$$P(D_i)=\exp[-\nu_i NSF(D_i)],$$

where $\nu_i=\frac{1}{N}$ is the partial volume of a voxel and $SF(D_i)$ is the survival fraction of clonogens exposed to dose D_i. EUD can be also calculated from the corresponding differential DVH. In this case ν_i is the relative size of the i'th dose bin corresponding to dose D_i and N is the number of bins.

Modeling cell survival has a long tradition and the most widely accepted model is the Linear-Quadratic (LQ) model. According to the LQ model, the surviving fraction of cells irradiated to dose D, $SF(D_i)$, for fractionated irradiation is calculated as

$$SF(D_i)=\exp\left[-D_i\left(\alpha+\beta\frac{D_i}{M}\right)\right], \quad (1)$$

where α and β are the parameters of the LQ model and M is the number of fractions. For perfectly uniform target dose distribution the same formulae can be used. That is,

$$P(EUD)=\exp[-NSF(EUD)]$$

and

$$SF(EUD)=\exp\left[-EUD\left(\alpha+\beta\frac{EUD}{M}\right)\right]$$

where EUD is the corresponding unknown equivalent dose. From the definition of EUD, the probabilities of tumor control for the inhomogeneous dose distribution and for the uniform dose distribution should be equal. Therefore, the following equation must hold:

$$\prod_{i=1}^{N}P(D_i)=P(EUD).$$

First, one can notice that the total number of clonogens, N, cancels out. That is, the formula holds for any density of clonogens or size of the tumor. Second, by taking twice the natural logarithm of both sides a quadratic equation for EUD is obtained:

$$EUD\left(\alpha+\beta\frac{EUD}{M}\right)=-\ln\sum_{i=1}^{N}\nu_i\exp\left[-D_i\left(\alpha+\beta\frac{D_i}{M}\right)\right].$$

This equation can be easily solved for EUD and dose-volume and dose per fraction effects can be studied for different tumor radiosensitivities (that is, for different values of α and β) and for different fractionation schemes (that is, for different values of M).

Based on various and admittedly incomplete clinical data the value of the parameter β for tumors is often an order of magnitude smaller than the value of the parameter α (with a possible notable exception of prostate carcinoma [31]). In this situation the quadratic term of the LQ model can be disregarded and the EUD formula simplifies to:

$$EUD=-\frac{\ln\sum_{i=1}^{N}\nu_i\exp(-\alpha D_i)}{\alpha} \quad (2)$$

If one prefers to describe cell radiosensitivity using SF_2 (the fraction of clonogens surviving a single dose of 2Gy) formula (2) has another form,

$$EUD=2Gy\frac{\ln\sum_{i=1}^{N}\nu_i(SF_2)^{Di/2Gy}}{\ln(SF_2)},$$

which is obtained by noticing that $SF_2=\exp(-2\alpha)$. Formula (2) has been proposed as a basic formula for optimization of dose distribution when the temporal distribution of dose is set and the only variable is the volumetric distribution of dose.

The value of EUD for any inhomogeneous target dose distribution is always bounded by the minimum target dose and the mean target dose. How close the EUD is to the minimum target dose depends on the value of α (or SF_2). For relatively radioresistant clonogens (i.e., for large values of SF_2 or small values of α) the EUD tends to the minimum target dose. For relatively radiosensitive clonogens (i.e., for small values of SF_2 or large values of α) the EUD tends to the mean target dose.

For normal structures we followed the concept of Damaged Volume (*DV*) that we investigated while developing our Critical Volume (CV) Normal Tissue Complication Probability (NTCP) model [13]. The concept of *DV* is based on two evident experimental facts. First, all normal organs and tissues have the ability to endure some level of damage caused by radiation before the clinically relevant manifestation of that damage occurs. Second, even at the dose levels considered "safe" for a normal organ some proportion of cells and sub-organ structures are killed or permanently damaged. A working hypothesis interpreting these observations is that a clinically relevant end-point occurs only when the proportion of killed cells or sub-organ structures exceeds some threshold level. This threshold level is specific for each normal structure and for each end-point of interest and is likely to vary in a population of patients.

Most normal structures are characterized by some tissue architecture. For example, a kidney is composed of nephrons, which in turn are composed of tubule cells. For modeling purposes it is convenient to describe a nephron using a concept of Functional Sub-Unit (FSU) introduced by Withers [26]. Indeed, it seems that each nephrons represents an independent structure performing a well-defined function. It was also observed by Withers that a single surviving tubule cell could regenerate a whole nephron. A similar well-defined architecture can be observed for lung with acini and alveoli. Organs or tissues that are not composed of clearly identifiable functional sub-structures (e.g., skin) can still be modeled using the same mathematical framework. That is, one can define an FSU as the largest volume (or surface in the case of skin) that can be rescued and repopulated by a single surviving cell.

A mathematical description of the modeling considerations of the previous paragraph is straightforward. If an FSU can be rescued by a single surviving cell then the probability of permanent damage of FSU depends on the dose, D, and the number of cells per FSU, n, according to binomial statistics as follows:

$$P_{FSU}(D,n)=[1-SF(D)]^n.$$

The probability of cell survival as a function of dose, $SF(D)$, can be calculated using, for example, formula (1), which is based on the LQ model. For a given inhomogeneous dose distribution the Damaged Volume (*DV*) is the proportion of destroyed FSUs. Assuming that the FSUs are uniformly distributed within the structure of interest the proportion of destroyed FSUs is the sum of destroyed FSUs calculated over all voxels within the structure divided by the total number of voxels m:

$$DV=1/m\sum_{i=1}^{m}P_{FSU}(D_i)=1/m\sum_{i=1}^{m}[1-SF(D_i)]^n. \quad (3)$$

The same number of FSU's is destroyed when the whole normal structure is uniformly irradiated to some dose EUD. Therefore, the following equation must hold:

$$1/m\sum_{i=1}^{m}[1-SF(D_i)]^n=[1-SF(EUD)]^n. \quad (4)$$

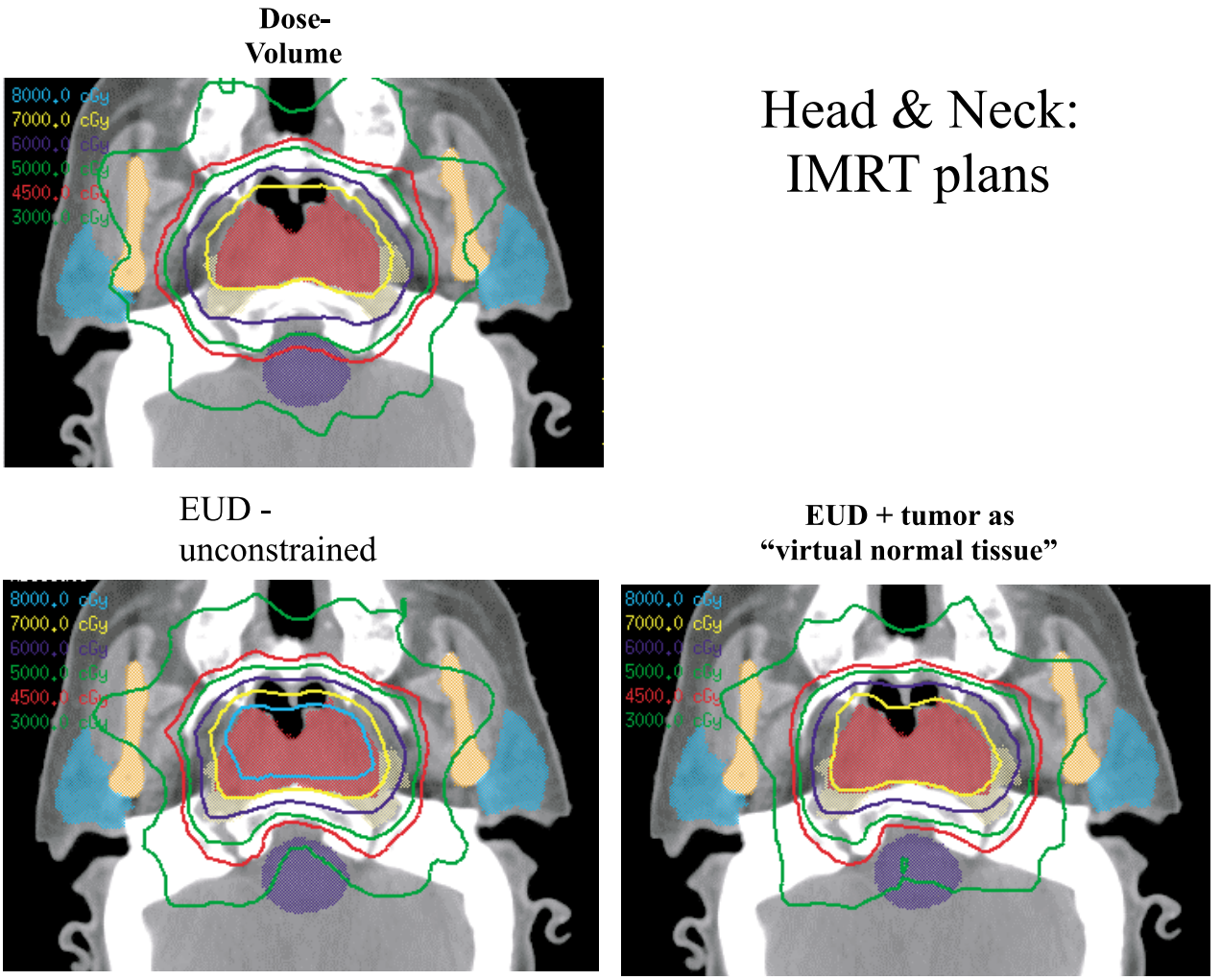

Figure 2. A color-wash display of dose distribution for a head and neck tumor for three planning approaches described in the text. The corresponding DVHs are shown in Figure 3.

This quadratic equation can be solved for EUD:

$$EUD=\frac{M}{2}\left[-\frac{\alpha}{\beta}+\sqrt{\left(\frac{\alpha}{\beta}\right)^2-\frac{4}{M\beta}\ln\left(1-DV^{\frac{1}{n}}\right)}\right], \qquad (5)$$

where M is the number of fractions. If the cell survival curve is assumed to be purely exponential (that is, if β is set to zero) equation (4) becomes linear in dose with a new solution

$$EUD=-\frac{\ln\left(1-DV^{\frac{1}{n}}\right)}{\alpha}. \qquad (6)$$

There are several advantages of the EUD concept. EUD is a physical dose but it also takes into account the radiosensitivity of irradiated tumor or normal cells. EUD represents a single number for each structure of interest and therefore it can be easily used to compare rival dose distributions. EUD can take into account not only volume effects but also fractionation effects [30]. EUD can be used as a single meta-meter of dose distribution for modeling the probabilities of tissue response to radiation (i.e., TCP and NTCP). EUD has been successfully applied to analyzing clinical data [32] and for optimization of IMRT plans [29, 33]. Figures 2 and 3 show an example of EUD-based optimized IMRT plan for head and neck cancer compared with IMRT plans optimized using standard dose and dose-volume-based objective functions and constraints. This example has been taken from one of our studies [29]. Figure 2 shows three dose distributions. Two of them correspond to EUD-based plans. One represents unrestricted maximization of the target EUD the other was obtained by assuming that there is some normal tissue within the target volume with its own tolerance and the corresponding probability of complication. All plans show very conformal dose distributions around the target volume and good sparing of both parotid glands and the spinal cord. Figures 3a-c show the corresponding DVHs for the target volume (Figure 3a), parotid glands (Figure 3b), and the spinal cord (Figure 3c). The EUD-based plans are clearly superior to the dose and dose-volume-based plan by sparing both critical normal structures more effectively while at the same time delivering more dose to the target volume. This was possible because the EUD-based approach implicitly maximizes the EUD for the target volume while minimizing the EUDs for the critical normal structures. The actual objective function that was used in these optimization examples represents maximization of the probability of local control and minimization of the probabilities of toxicity for critical normal structures by using the corresponding EUDs as variables of the dose-response functions defined for each VOI [29, 33]. The EUD-based optimization has the flexibility to explore a much wider space of possible dose distributions that dose-based optimization. That is, it can find solutions that may not be found or may not be apparent when using a dose-based approach.

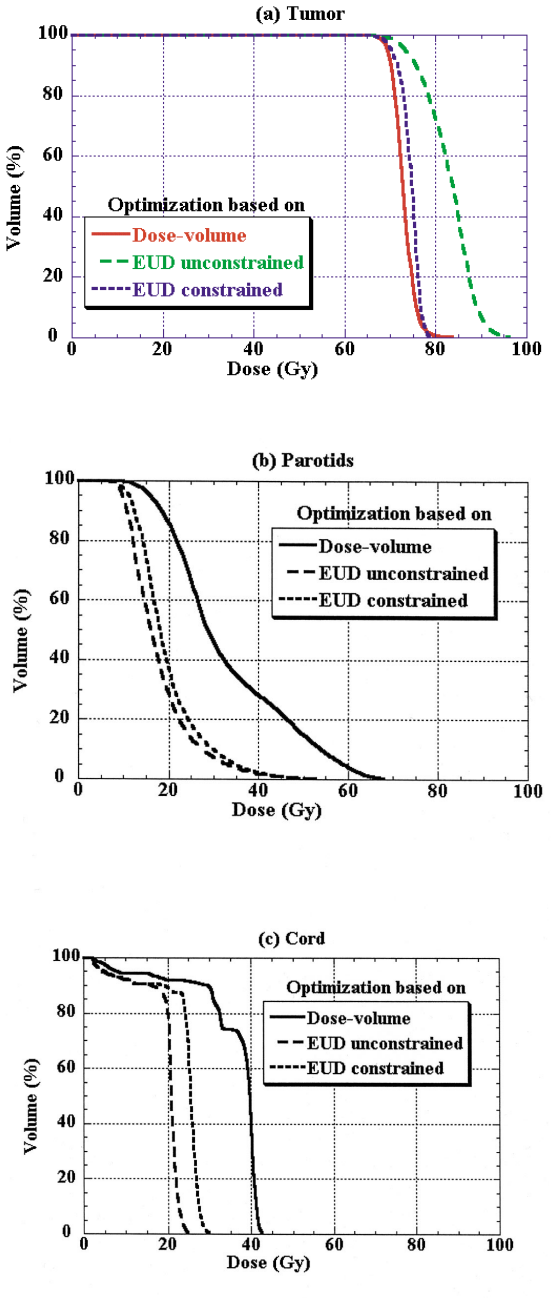

Figure 3. DVHs for the head and neck tumor shown in Figure 2. Solid lines corresponds to dose and dose-volume-based optimization, dashed lines correspond to unconstrained EUD-based optimization, dotted lines correspond to constrained EUD-based optimization: a) target DVHs, b) parotid glands DVHs, c) spinal cord DVH

Conclusions

Modern radiation therapy planning requires tools that take into account multidimensional (i.e., volumetric and temporal) aspects of dose distributions and biological and clinical consequences of radiation treatment. An example of such tools, an EUD concept based on cell survival and tissue architecture, has been described here. It has been shown here and elsewhere that EUD is useful for reporting, evaluating and optimizing treatment plans. The EUD can be used directly to describe the biologically equivalent dose that each VOI receives under any (inhomogeneous) treatment conditions. The EUD can also be used as a meta-meter for modeling the probability of tumor control and the probability of toxicity for normal critical organs and tissues.

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