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# **The Use and QA of Biologically Related Models for Treatment Planning**

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**Report of AAPM Task Group 166  
of the Therapy Physics Committee**

**March 2012**

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ISBN: 978-1-936366-13-2  
ISSN: 0271-7344

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Published by

American Association of Physicists in Medicine  
One Physics Ellipse  
College Park, MD 20740-3846

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Short report published in *Medical Physics*, vol 39, No. 3, 2012

## **Abstract**

Treatment planning tools that use biologically related models for plan optimization and/or evaluation are being introduced for clinical use. A variety of dose response models and quantities along with a series of organ-specific model parameters are included in these tools. However, due to various limitations, such as the limitations of models and available model parameters, the incomplete understanding of dose responses, and the inadequate clinical data, the use of a biologically based treatment planning system (BBTPS) represents a paradigm shift and can be potentially dangerous. There will be a steep learning curve for most planners. The purpose of this task group (TG) is to address some of these relevant issues before the use of BBTPS becomes widely spread. In this report, we (1) review the biologically related models including both used and potentially to be used in treatment planning process; (2) discuss strategies, limitations, conditions, and cautions for using biologically based models and parameters in clinical treatment planning; (3) demonstrate the practical use of the three commercially available BBTPSs and potential dosimetric differences between biologically model-based and dose-volume (DV)-based treatment plan optimization and evaluation; (4) identify the desirable features and future directions in developing BBTPS; and (5) provide general guidelines and methodology for the acceptance testing, commissioning, and routine quality assurance (QA) of BBTPS.

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## List of Symbols and Abbreviations Used in this Report

3D	three-dimensional
3DCRT	three-dimensional conformal radiation therapy
AAPM	American Association of Physicists in Medicine
AP/PA	anterior-posterior/posterior-anterior
ASTRO	American Society for Radiation Oncology
BBTP	biologically based treatment planning
BBTPS	biologically based treatment planning system
BGRT	biologically guided radiation therapy
CDF	cumulative distribution function
CERR	Computational Environment for Radiotherapy Research
cEUD	cell killing-based equivalent uniform dose
CPF	complication probability factor
CRCAE	Common Terminology Criteria for Adverse Events
CRE	cumulative radiation effect
CTV	clinical target volume
DICOM	Digital Imaging and Communications in Medicine
DSB	double-strand break
DV	dose volume
DVH	dose-volume histogram
EORTC	European Organization for Research and Treatment of Cancer
EUD	equivalent uniform dose
fDVH	functional DVH
FSU	functional subunit
gEUD	generalized EUD
GTV	gross tumor volume
IMRT	intensity-modulated radiation therapy

LKB	Lyman-Kutcher-Burman (model)
LQ	linear quadratic
MLD	mean lung dose
NSD	nominal standard dose
NTCP	normal tissue complication probability
OAR	organ at risk
P+	complication-free cure
PDD	percentage depth dose
PET	positron emission tomography
PRV	planning organ at risk volume
PTV	planning target volume
QA	quality assurance
QUANTEC	QUantitative Analysis of Normal Tissue Effects in the Clinic
ROI	region of interest
RT	radiation therapy
ROG	Radiation Oncology Therapy Group
SBRT	stereotactic body radiation therapy
SF	surviving fraction
SRS	stereotactic radiosurgery
TCP	tumor control probability
TD	time dose
TDF	time dose fractionation
TPS	treatment planning system
UTCP	uncomplicated TCP
V <sub>x</sub>	volume receiving at least dose x in Gy

## I. INTRODUCTION

The goal of radiation therapy (RT) is to deliver a therapeutic dose of radiation to target tissues while minimizing the risks of normal tissue complications. Until recently, the quality of a radiation treatment plan has been judged by physical quantities, i.e., dose and dose-volume (DV) parameters, thought to correlate with biological response rather than by estimates of the biological outcome itself. It is widely recognized that the DV criteria, which are merely surrogate measures of biological responses, should be replaced by biological indices in order for the treatment process to more closely reflect clinical goals of RT (Ling and Li 2005). Developments in our understanding of advantages and limitations of existing dose-response models begin to allow the incorporation of biological concepts into a routine treatment planning process.

### I.A. BRIEF REVIEW OF THE HISTORY AND SIGNIFICANCE OF DOSE-RESPONSE MODELING FOR TREATMENT PLANNING

In the early days of radiation oncology, the biological consequences of treatment were judged mainly by the dose absorbed in the tumor and surrounding normal tissues, with experience-driven accounting for overall treatment time and fractionation. To correct for the latter two factors nominal standard dose (NSD), cumulative radiation effect (CRE), and time dose fractionation (TDF) formalisms were developed (Strandqvist 1944; Ellis 1969; Kirk et al. 1971; Orton and Ellis 1973). These concepts, while serving a practical purpose, were statistical in nature and were not based on clear radiobiological principles. Progress in basic radiobiology in the mid of the last century has led to the formulation of first models of cell killing and, eventually, to models that linked radiation sensitivity to cure rates for tumors. One of the first such formalisms was proposed by Munro and Gilbert (1961). Although the radiobiological complexity of models to describe cell survival, which are an essential part of any mechanistic tumor control probability (TCP) model, varied significantly among different investigators, the assumption that a number of surviving cells follows the Poisson distribution (section II.D) put forward by Munro and Gilbert (1961) to this day remains a basis of the majority of biologically based TCP models.

The roots of normal tissue complication probability (NTCP) modeling lie in attempts to quantify dependence of tolerance dose for a certain radiation effect on the size of the treated region (reviewed in Schultheiss et al. 1983). A power-law relationship between irradiated volume and tolerance dose (section II.F.1) formulated in these early studies remains an important component of many present-day concepts. NTCP modeling gained more attention with the advent of three-dimensional conformal radiation therapy (3DCRT). Highly non-homogenous dose distributions in organs at risk (OARs) obtained with 3DCRT required additional tools to help collapse complex dose distributions into a single metric that correlates with the risk of radiation injury. One of the first metrics to take into account the non-homogeneous nature of a dose distribution was a complication probability factor (CPF) proposed by Dritschilo et al. (1978). Subsequent efforts involved attempts to include additional radiobiological details into the modeling process [e.g., Källman et al. (1992b), Jackson et al. (1993), Niemierko and Goitein (1993)], although empirical models have also found their niche (e.g., Lyman 1985). For additional information regarding early applications of biological modeling in treatment planning, the reader is referred to a review by Orton et al. (2008).

Several radiotherapy centers incorporated dose-response modeling into their dose-escalation protocols. TCP and NTCP models (Ten Haken et al. 1993; Jackson et al. 1996; Mehta et al. 2001) have been used to guide safe dose escalation for non-small-cell lung cancer (Robertson et al. 1997; Hayman et al. 2001; Rosenzweig et al. 2005; Adkison et al. 2008) and hepatic tumors (McGinn et al. 1998; Ben-Josef et al. 2005; Dawson et al. 2006). Song et al. (2005) used an NTCP model to guide prescription dose selection for stereotactic body radiation therapy (SBRT) of lung tumors. Many investigators incorporated TCP and NTCP models into in-house computer programs for *evaluation* of treatment plans [e.g., Sanchez-Nieto and Nahum (2000), Warkentin et al. (2004)]. Although absolute values of predicted outcome probabilities may not yet be reliable, such tools might provide useful information when alternate treatment plans are compared, particularly in cases where dosimetric advantages of one plan over another is not clear-cut according to DV criteria (Kutcher et al. 1991). However, this view has been questioned (Langer et al. 1998) suggesting that caution should be exercised even when using TCP/NTCP indices in a relative sense to rank treatment plans. Because of doubts in robustness of model predictions and accuracy of parameter values, biologically based plan evaluation tools have not yet found a widespread use in commercial treatment planning systems (TPSs).

Another great potential of radiobiological modeling lies in the use of models to construct cost functions for *optimization* of treatment plans. Early attempts involve optimization of dose distributions outside of the tumor volume based on the CPF concept (Wolbarst et al. 1980). When more sophisticated dose-response models were proposed, several research groups investigated the possibility of using cost functions comprised of TCP and NTCP for optimization of treatment plans (Källman et al. 1992a; Mohan et al. 1992; Niemierko et al. 1992; Söderström and Brahme 1993; Wang et al. 1995). For example, the concept of “complication-free cure,” denoted as  $P_+$ , was suggested as a cost function for unconstrained biologically based optimization (Brahme et al. 1991). Despite the potential benefits of TCP/NTCP-based optimization outlined in these studies, it was widely recognized that much more additional work was needed to increase confidence in the biologically based treatment planning approach (Bortfeld et al. 1996; Mohan and Wang 1996). A concept of the equivalent uniform dose (EUD) [including the generalized EUD (gEUD)] proposed by Niemierko (1997, 1999) has found considerable support among proponents of biologically based optimization because it offers a compromise between purely biological indices, such as TCP and NTCP, and traditional DV metrics. Many investigators have demonstrated that incorporating EUD-based cost functions into inverse treatment planning algorithms for the optimization of intensity-modulated radiation therapy (IMRT) plans may result in improved sparing of OARs without sacrificing target coverage (Wu et al. 2002, 2003, 2005; Thieke et al. 2003; Stavrev et al. 2003; Yang and Xing 2004; Thomas et al. 2005; Chapet et al. 2005; Spalding et al. 2007). Several studies reported that optimization of IMRT plans based on a mixture of EUD-based and DV-based cost functions is a robust way to obtain desired dose distributions. This approach is therefore attractive for the purposes of the commercial implementations of biological models for treatment planning (section IV).

## I.B. LIMITATIONS OF CURRENTLY USED DOSE-VOLUME-BASED TREATMENT PLANNING

Single or multiple DV constraints used for inverse treatment planning or plan evaluation are based on clinical studies that demonstrate correlation between tumor control/complication incidence and particular DV metrics. For example  $V_{20}$  (percentage of lung volume receiving at least 20 Gy) is used to gauge the probability of a plan causing grade  $\geq 2$  or grade  $\geq 3$  radiation pneumonitis (Graham et al. 1999). There are a number of limitations associated with this approach: (1) Typically more than one point on the DVH (e.g.,  $V_5$ ,  $V_{40}$ , mean lung dose) correlates with the complication. This correlation is however specific to treatment delivery technique, i.e., IMRT or 3DCRT, beam arrangements, etc. Marks et al. (2010) in their recent QUANTEC (section II.G) report on radiation effects in lung noted that “the correlations between dosimetric parameters are technique dependent, and readers should carefully assess the similarity of their treatment technique to the historical reports before using any of these limits as clinical constraints.” (2) Generally, optimization with DV constraints is indirect, requiring substantial skill in selecting values and relative weights for constraints that provided optimal TCP and NTCP values. With typically 1 to 3 constraints, a range of optimized normal tissue DVHs that comply equally well with these few constraints but carry distinctly different risk of complications is possible. When biological methods are also used in the optimization, then DV points may be replaced with a function that more efficiently drives the shape of the DVH curves to achieve the plan leading to the most favorable overall treatment outcome, rather than satisfying the applied constraints. (3) Specifying multiple DV constraints increases computational complexity of the inverse treatment planning problem. Moreover, cost functions based on DV constraints can lead to multiple local minima (Deasy 1997; Wu and Mohan 2002). This implies that a search algorithm designed for global minimum problems is likely to get trapped in a local minimum, potentially leading to less favorable dose distributions.

Most current systems that use DV-based plan optimization also lack tools for routinely evaluating biologically based metrics alongside DVH metrics. These tools are an important step for developing datasets that demonstrate intra-clinic correlation with outcomes, and comparisons with conventional DV point constraint optimization. Since dose distributions for plans driven by biological methods’ constraints may differ substantially from those driven by DV point constraints, evaluation tools are important as a basis for progression to preferentially adopting biological methods in optimization.

## I.C. SCOPE AND TERMINOLOGY

Historically, dose prescription in RT has been performed using population-based knowledge about behavior of a particular type of tumor or normal tissue. Rapid advances in functional imaging, molecular techniques, predictive assays, and RT delivery technology will sooner or later enable implementing truly-individualized RT in the clinic (Stewart and Li 2007). This task group report (TG-166) will refer to a framework of RT that takes advantage of information about spatial and temporal distribution of relevant patient-specific biological parameters, such as tumor and normal cell radiosensitivity, oxygenation status, proliferation rate, etc., as **biologically guided radiation therapy (BGRT)**. Other investigators have previously used various alternate

terms to describe the same basic concept, e.g., radiobiologically optimized radiation therapy (Brahme 1999), multidimensional conformal radiotherapy (Ling et al. 2000), biologically conformal radiation therapy (Yang and Xing 2005), biologically based radiation treatment planning (Ling and Li 2005), theragnostic imaging (Bentzen 2005), and risk-adaptive optimization (Kim and Tomé 2006).

An integral part of BGRT is the ability to design dose distributions that would produce the desired balance between tumor cure and normal tissue injury based on the knowledge of biological properties of the particular tumor and surrounding normal tissues. Such a multidimensional problem is most appropriately addressed in the framework of inverse treatment planning presently employed for the optimization of IMRT plans and will rely on models to describe relationships between dose distributions and biological outcomes. This TG report will refer to any use of biological response models that involves feedback from a model during the treatment planning process as **biologically based treatment planning (BBTP)**. The feedback may be either passive/automated in the case of inverse treatment planning, or with active participation from the planner in the case of forward treatment planning.

Whereas future development of BGRT relies on sufficient advances in methods to obtain individualized biological parameters, BBTP has already started to enter clinical practice. BBTP is viewed as a subset of BGRT. However, BGRT is more than just BBTP based on patient-specific biological parameters; BGRT will employ biological models not only at the time of initial planning, but also to adapt treatment based on tumor/OAR response to RT (e.g., Søvik et al. 2007). For a detailed discussion on BGRT and BBTP, readers are referred to a vision 20/20 paper by Stewart and Li (2007). The scope of this report is limited to BBTP, i.e., the use of biological models for plan optimization and evaluation in external beam radiation therapy. The emphasis is made on the models that are implemented or may potentially be implemented in commercial TPSs.

The following definitions and terms are used in this report:

*Plan optimization or inverse planning:* the process of generating an optimal plan following the desired objectives. The planner specifies objectives (i.e., optimization criteria) including constraints (limits that should not be violated) and goals for both the target and normal structures. Internally, the planning system represents these objectives in a cost function, which must be maximized or minimized by an optimization algorithm.

*Tumor control or local control:* no evidence of tumor recurrence in the region treated with a definitive intent.

*Normal tissue complication:* an unfavorable symptom, sign, or disease temporally associated with the use of radiation therapy. The Common Terminology Criteria for Adverse Events (CTCAE) (<http://ctep.cancer.gov>) or EORTC/RTOG scale (Cox et al. 1995) is commonly used for grading normal tissue complications.

*Functional subunit (FSU):* structurally or functionally discrete tissue elements (Withers et al. 1988), e.g., nephrons in kidney or alveoli in lung.

*Volume effect:* modification of normal tissue/organ tolerance with a change in irradiated volume. That is, the tolerance dose increases to a degree that depends on the tissue and complication endpoint as the irradiated volume decreases. The magnitude of the volume effect depends, at least in part, on an underlying anatomic/biological structure of the organ.



*Parallel organ:* normal organ in which each FSU functions relatively independently and damage to a sufficiently small region does not render the whole organ dysfunctional. Consequently, a volume threshold or functional reserve may exist. Examples are lung, kidney, and liver.

*Serial organ:* normal organ in which FSU are structured in a series; if one FSU is incapacitated, the organ will exhibit complications. Examples are spinal cord, intestines, and optic nerve.

*Serial and parallel response:* normal organ response characterized by small and large volume dependence, respectively. The connection between organ architecture designated as serial or parallel (see above) and serial or parallel response is not always exact. Nevertheless within the framework of this report, an exact correspondence between organ architecture and response is assumed. This means that in parallel organs complications are assumed to occur after a substantial fraction of FSUs are damaged, volume effect is large, and response is “parallel.” In contrast, a serial organ would exhibit complications after a single FSU is incapacitated, volume effect is small, and response is “serial.”

## II. DOSE RESPONSE MODELS

The field of study of mathematical models of tumor and normal tissue responses to dose is extensive and beyond the scope of this report to explore fully. The present treatment is intended to provide the reader with perspective on the models and parameters typically encountered in BBTP along with references helpful to further exploration. Supplemental information is presented in the appendices.

### II.A. GENERALIZED EQUIVALENT UNIFORM DOSE (gEUD)

The concept of equivalent uniform dose (EUD) proposed by Niemierko (Niemierko 1997) provides a single metric for reporting non-uniform tumor dose distributions. It is defined as the uniform dose that, if delivered over the same number of fractions as the non-uniform dose distribution of interest, yields the same radiobiological effect. To extend the concept of EUD to normal tissues, Niemierko (1999) proposed a phenomenological formula referred to as the generalized EUD, or gEUD:

$$\text{gEUD} = \left( \sum_i v_i D_i^a \right)^{1/a}, \quad (1)$$

where  $v_i$  is the fractional organ volume receiving a dose  $D_i$  and  $a$  is a tissue-specific parameter that describes the volume effect. For  $a \rightarrow -\infty$ , gEUD approaches the minimum dose; thus negative values of  $a$  are used for tumors. For  $a \rightarrow +\infty$ , gEUD approaches the maximum dose (serial organs). For  $a = 1$ , gEUD is equal to the arithmetic mean dose. For  $a = 0$ , gEUD is equal to the geometric mean dose. The cell killing-based EUD (cEUD, appendix A) has a more mechanistic background than the gEUD. However the gEUD is often used in plan evaluation and optimization because the same functional form can be applied to both targets and OARs with a single parameter capturing (it is hoped) the dosimetric “essence” of the biological response.

## II.B. LINEAR-QUADRATIC (LQ) MODEL

The linear-quadratic (LQ) formalism is most commonly used to model cell survival. Radiation-induced reproductive cell death has been conclusively linked to DNA damage, specifically to DNA double-strand breaks (DSB). In cellular environment, DSB dose-response is linear up to very high doses (40 to 50 Gy) and approximately 40 to 50 DSB are produced per Gy (Sachs et al. 1997). Most DSB are faithfully repaired; however, some undergo binary misrepair, which may lead to a production of a lethal lesion, while some fail to get repaired. Induction, repair, and misrepair of DSB and formation of lethal lesions as a function of dose rate and time can be described as a system of differential equations (Sachs et al. 1997). This led to development of kinetic reaction-rate models, lethal-potentially-lethal (Curtis 1986) and repair-misrepair (Tobias 1985). The solution to these equations to derive dose-response for lethal lesions takes a complex form and is available for only specific situations; for example, instantaneous dose delivery followed by full repair. It has been demonstrated that for doses and dose rates of relevance to radiation therapy, with a possible exception of doses per fraction used in SBRT, i.e., in excess of 10 Gy per fraction, the yield of lethal lesions can be well approximated by an LQ function of dose. That is, the fraction of cells surviving irradiation to a dose  $D$  in  $n$  fractions can be approximated as

$$S = \exp\left(-\alpha D - \beta \frac{D^2}{n}\right), \quad (2)$$

where  $\alpha$  and  $\beta$  are the proportionality coefficients for the linear and quadratic components, respectively. Effects of repopulation (appendix B) and repair (not discussed) may be reflected as additional terms within the exponent, but Eq. (2) is most commonly encountered.

Validity of the LQ model for large doses per fraction encountered in radiosurgery and SBRT has become a matter of ongoing debate (Marks 1995; Hall and Brenner 1995; Brenner 2008; Kirkpatrick et al. 2008; Fowler 2008). The issue of contention is that the LQ formalism predicts a continuously bending survival curve while experimental data clearly demonstrate that at large doses the surviving fraction becomes an exponential function of dose; i.e., follows a straight line on a semi-log plot. Hybrid solutions accounting for this effect have been suggested (Park et al. 2008). Despite these controversies, the LQ model remains a tool of choice for isoeffect calculations in conventionally fractionated photon beam therapy.

## II.C. LQ-BASED CORRECTION OF DOSE-VOLUME HISTOGRAMS

To account for variations in dose per fraction in different subvolumes of a target or an OAR with changes in fractionation schedules, total physical dose corresponding to each DVH bin,  $D_i$ , is sometimes converted into isoeffective dose in 2-Gy fractions using the equation (Wheldon et al. 1998; Yorke 2001):

$$\text{LQED}_{2_i} = D_i \frac{1 + \frac{D_i/n}{\alpha/\beta}}{1 + \frac{2}{\alpha/\beta}}, \quad (3)$$



where  $n$  is the number of fractions. This procedure requires one parameter, the  $\alpha/\beta$  ratio, which is typically assumed to be equal to 3 Gy for late-responding normal tissues and 10 Gy for tumors and early responding normal tissues. In general literature, radiation responses were typically determined for 2-Gy fractions. It is thus a good practice to utilize LQED2 rather than  $D$  in calculations of NTCP and TCP.

## II.D. COMMON TCP MODELS

A majority of mechanistic TCP models are based on the assumption that the number of surviving clonogenic tumor cells, i.e., cells capable of regrowing the tumor, follows the Poisson distribution (Munro and Gilbert 1961). A unicellular hypothesis, i.e., a single surviving clonogen is sufficient to regrow the tumor is further invoked. If the initial number of clonogens is  $N$ , the average number of surviving clonogens is given by  $SN$ , where  $S$  is the overall surviving fraction after a course of radiation therapy; e.g., Eq. (2). The probability of tumor control is then equal to the probability that no clonogens survive:

$$\text{TCP} = \exp(-SN). \quad (4)$$

TCP can be approximated by any two-parameter mathematical function representing a sigmoid-shaped curve. In commonly used empirical TCP models these two parameters are  $D_{50}$ , the dose at which 50% of tumors are controlled, and normalized dose-response gradient  $\gamma = D \frac{d\text{TCP}}{dD}$  evaluated at  $D = D_{50}$  (Brahme 1984). In practice, parameter details sufficient for a fully described mechanistic model, such as  $N$  or the distribution of  $\alpha$  (appendix B) are often unavailable. Therefore, even mechanistic models approximate these parameters with empirical approximations.

The Poisson assumption [Eq. (4)] has limitations when clonogen repopulation occurs during treatment. One obvious problem is that simple application of exponential tumor growth predicts that all tumors recur at sufficiently long times after external beam treatment or for permanent implants with exponentially decaying sources (Zaider and Minerbo 2000). Some investigators have proposed TCP models based on detailed descriptions of clonogen proliferation kinetics (Tucker and Taylor 1996; Zaider and Minerbo 2000). Such non-Poisson models, however, lack simple analytical solutions, which has limited their applications in BBTP.

In general, TCP is formulated as a product over the structure's voxels weighted probability functions:

$$\text{TCP} = \prod_{i=1}^M P(D_i)^{v_i}, \quad (5)$$

where  $M$  is the number of voxels and the relative volume of the voxel is  $v_i = V_i/V_{\text{ref}}$ . For practical calculations, bins of a differential DVH,  $(D_i, v_i)$ , may be used. Several formulations of the probability are commonly encountered. One (Lind et al. 1999) uses the LQ model:

$$P(D_i) = \exp\left(-\exp\left(e\gamma - \alpha D_i - \beta \frac{D_i^2}{n}\right)\right). \quad (6)$$

Here, the number of clonogens,  $N$ , is approximated by  $\exp(e\gamma)$ . In Eq. (6),  $\gamma$  is the normalized dose-response gradient at the dose, where the absolute dose-response gradient is the steepest. The expression  $N = \exp(e\gamma)$  is exact when  $\beta = 0$  or while the dose per fraction remains constant and constitutes a very close approximation otherwise (Bentzen and Tucker 1997). Given input values of  $D_{50}$ ,  $\gamma$ , and  $\alpha/\beta$ , individual values for  $\alpha$  and  $\beta$  are calculated as

$$\alpha = \frac{e\gamma - \ln(\ln 2)}{D_{50} \left(1 + \frac{2}{\alpha/\beta}\right)} \quad (7)$$

and

$$\beta = \frac{e\gamma - \ln(\ln 2)}{D_{50} (\alpha/\beta + 2)}. \quad (8)$$

Another formulation is a linear-Poisson formulation (Lind et al. 1999):

$$P(D_i) = \exp \left( -\exp \left( e\gamma - \frac{D_i}{D_{50}} (e\gamma - \ln(\ln 2)) \right) \right). \quad (9)$$

If the dose at each voxel is converted to its equivalent dose for a 2-Gy fraction using the LQ equation [Eq. (3)] and that dose (LQED2<sub>*i*</sub>) is substituted for  $D_i$  in Eq. (9), the result is equivalent to Eq. (6). These are the most commonly encountered formulations used for calculating the TCP among the treatment planning systems examined in this report.

The logistic function is a popular choice to describe the sigmoid shape dose-response in empirical TCP models. For example, Okunieff et al. (1995) used:

$$P(D_i) = \frac{\exp[(D_i - D_{50})/k]}{1 + \exp[(D_i - D_{50})/k]}, \quad (10)$$

where  $k$  is related to the normalized dose-response gradient according to  $k = D_{50}/(4\gamma)$ . The empirical log-logistic function (Schultheiss et al. 1983; Niemierko and Goitein 1991):

$$P(D_i) = \frac{1}{1 + (D_{50}/D_i)^k}, \quad (11)$$

where  $k$  controls the slope of the curve. This formulation is recommended in AAPM Report 137 (Nath et al. 2009) for use with brachytherapy sources.

## II.E. AVAILABILITY OF TCP MODEL PARAMETERS

Okunieff et al. (1995) have collected and analyzed dose-response data for local control of various tumors treated with adjuvant intent (control of microscopic disease) and with curative intent (control of gross disease). Equation (10) was fit to the data, and estimates of  $D_{50}$  and  $\gamma$  were reported for 62 dose-response curves for the control of macroscopic disease and 28 dose-response curves for the control of microscopic disease. Parameter estimates for the Poisson

statistics-based model [Eqs. (B1) or (B2)] have been obtained for head & neck tumors (Roberts and Hendry 1993; Wu et al. 1997), breast tumors (Brenner et al. 1993; Guerrero and Li 2003), malignant melanoma (Brenner 1993), squamous cell carcinoma of the respiratory and upper digestive tracts (Brenner 1993), prostate cancer (Brenner and Hall 1999; Wang et al. 2003), brain tumors (Qi et al. 2006), rectal cancer (Suwinski et al. 2007), and liver cancer (Tai et al. 2008). The Poisson-based model incorporating distribution of interpatient radiosensitivity [Eq. (B3)] has been used to refit previously analyzed datasets (Brenner 1993; Brenner and Hall 1999) for breast cancer, melanoma, tumors of the respiratory and upper digestive tracts (Webb 1994), and prostate cancer (Nahum et al. 2003).

## II.F. COMMON NTCP MODELS

The notion of volume effects is the cornerstone of efforts to model dose-response relationships for normal tissues. In parallel organs, considerable sparing of organ function is afforded by reducing the irradiated volume and their response is well correlated with a mean organ dose. In contrast, serial organs typically exhibit threshold-like responses to radiation and little, if any, modulation of the response is obtained by reducing the volume of organ irradiated. Their response is generally well correlated with a maximum organ dose or the “hot spot.” A robust model should accurately describe dose-response of incidence of complications as well as properly account for volume effect. Briefly presented below are NTCP models commonly used in BBTP. Serial (critical element) and parallel (critical volume) organ models are described in appendix C.

### II.F.I. Lyman-Kutcher-Burman (LKB) Model

The Lyman model (Lyman 1985) was designed to describe complication probabilities for uniformly irradiated whole or partial organ volumes. The cumulative distribution function (CDF) of the normal distribution is chosen to represent an empirical sigmoid dependence of NTCP on dose. Two parameters,  $TD_{50}$  and  $m$ , describe the position of the sigmoid curve along the dose axis and curve steepness, respectively. A third parameter,  $n$ , describes the magnitude of the volume effect using a power-law relationship between the tolerance dose and irradiated volume:

$$TD(V) = TD(1)/V^n. \quad (12)$$

Here,  $n$  is related with parameter  $a$  in Eq. (1) as  $n = 1/a$ ,  $TD(V)$  is the tolerance dose for a given partial volume fraction  $V$ , and  $TD(1)$  is the tolerance dose for the full volume. Small values of  $n$  correspond to small volume effects (“serial” effects) and large values correspond to large (parallel) volume effects. Although  $n \leq 1$  is used for the earliest applications of the Lyman model (Burman et al. 1991), this is not a physical or biological restriction and many recent analyses find best fits to complications data with  $n > 1$ .

Because the Lyman model is defined for uniform irradiation and normal tissues are rarely irradiated uniformly, several algorithms (DVH-reduction algorithms) to convert a heterogeneous dose distribution into a uniform partial or whole organ irradiation resulting in the same NTCP have been designed [see Hamilton et al. (1992) and Cozzi et al. (2000) for an overview]. Among these the effective volume method (Kutcher and Burman 1989) is most commonly used to

complement the Lyman model. The combined formalism is often referred to as the Lyman-Kutcher-Burman (LKB) model (e.g., Deasy 2000).

A mathematically equivalent but more conceptually transparent formulation of the LKB model was first proposed by Mohan et al. (1992). According to this model, NTCP is calculated using the following equations:

$$\text{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t e^{-\frac{x^2}{2}} dx \quad (13)$$

$$t = \frac{D_{\text{eff}} - TD_{50}}{mTD_{50}} \quad (14)$$

$$D_{\text{eff}} = \left( \sum_i v_i D_i^{1/n} \right)^n, \quad (15)$$

where  $D_{\text{eff}}$  is the dose that, if given uniformly to the entire volume, will lead to the same NTCP as the actual non-uniform dose distribution,  $TD_{50}$  is the uniform dose given to the entire organ that results in 50% complication risk,  $m$  is a measure of the slope of the sigmoid curve,  $n$  is the volume effect parameter, and  $v_i$  is the fractional organ volume receiving a dose  $D_i$ . Note that  $D_{\text{eff}}$  is conceptually identical to the gEUD [Eq. (1)] with parameter  $a = 1/n$ . To account for differences in dose per fractionation, it is common to replace  $D_i$  with the equivalent dose delivered in 2-Gy fractions, LQED2 [Eq. (3)]. For a derivation of Eqs. (13)–(15) from the Lyman model (Lyman 1985) and the Kutcher-Burman DVH reduction scheme (Kutcher and Burman 1989), see Deasy (2000), Li et al. (2003), and Luxton et al. (2008).

### II.F.2. Relative Seriality Model

The relative seriality model or the  $s$ -model (Källman et al. 1992b) describes response of an organ with a mixture of serial- and parallel-arranged FSUs. The relative contribution of each type of architecture is described by the parameter  $s$ , which is equal to unity for a fully serial organ and zero for a fully parallel organ. NTCP is given by the following equation [see Källman et al. 1992b for details]:

$$\text{NTCP} = \left\{ 1 - \prod_i \left[ 1 - P(D_i)^s \right]^{v_i} \right\}^{1/s}, \quad (16)$$

where  $v_i$  is the fractional organ volume receiving a dose  $D_i$  and  $P(D_i)$  is the complication. Although the relative seriality model has been designed using mechanistic tissue architecture principles, in practice values of the parameter  $s$  found to provide best fits to clinical data often exceed the theoretical maximum of unity, which prompted suggestions to consider the model phenomenological (Stavreva and Stavrev 2002). The Poisson model for  $P(D_i)$  [Eqs. (6)–(8)], are often used in TPSs for calculation of NTCP.

### II.F.3. Other NTCP Models

Some alternative NTCP modeling approaches have been proposed to improve the accuracy of complication risk predictions. These models have the potential to be used in future BBTP efforts and therefore warrant a brief mention. Although DV metrics usually show the strongest correlations with complication incidence compared to demographic and clinical variables, the inclusion of non-dosimetric factors into NTCP models has been shown to increase their predictive power. For example, more accurate predictions of radiation pneumonitis risk have been obtained when plasma levels of transforming growth factor  $\beta$  (Fu et al. 2001), tumor position along the cranio-caudal axis (Hope et al. 2006), or smoking status (Tucker et al. 2008) were added to dosimetric parameters. In another example, the use of concurrent chemotherapy provides an independent predictive factor of acute esophageal toxicity in lung cancer patients and, when combined with dosimetric factors, helps to more accurately estimate patients' risks (Bradley et al. 2004; Belderbos et al. 2005). NTCP analyses based on patient populations with incomplete follow-up may substantially underestimate complication risks. At the expense of additional adjustable parameters, the effect of censoring can be taken into account, resulting in potentially more accurate NTCP estimates (Tucker et al. 2008). The majority of current NTCP models are DVH-based and therefore ignore important information about location of cold and hot spots within an OAR. The so-called "cluster models" (Thames et al. 2004; Tucker et al. 2006) are based on the assumption that not only volume, but also spatial distribution of hot spots affect complication risks. These models provide a first step toward a new class of NTCP models that would take into account the entire three-dimensional (3D) dose distribution, and may further improve the accuracy of NTCP estimates.

### II.G. AVAILABILITY OF NTCP MODEL PARAMETERS AND QUANTEC SURVEY

The modern knowledge of normal tissue tolerance was summarized in the seminal publication by Emami et al. (1991). The authors compiled tolerance dose values for uniform whole- and partial-organ irradiation of 28 critical structures based on available literature and personal experience. In an accompanying article, Burman et al. (1991) fit the Lyman model (section II.F.1) to the Emami et al., tolerance data. In the past 18 years, many investigators tested NTCP predictions based on the Emami et al., and Burman et al., reports against new clinical data and/or provided new parameter estimates for various NTCP models. Most data have been collected for the lung, parotid glands, liver, rectum, and esophagus (Kong et al. 2007; Milano et al. 2007 and references therein); information about other organs, albeit less abundant, is also available. Several attempts have been made to obtain NTCP model parameters based on pooled data from different institutions (e.g., Kwa et al. 1998; Rancati et al. 2004; Tucker et al. 2007; Semenenko and Li 2008). However, it is recognized that many limitations are inherent in extracting/pooling data from the literature. That is, variations in endpoint definitions/grading scales, fractionation schedules, patient populations, dosimetry, etc., among different studies have to be reconciled. Regardless of these difficulties, there is an urgent need to summarize the new normal tissue toxicity data in a clinically useful manner.

QUANTEC (QUantitative Analysis of Normal Tissue Effects in the Clinic) is a multidisciplinary effort jointly funded by the American Association of Physicists in Medicine (AAPM)

and the American Society for Radiation Oncology (ASTRO), which aims to summarize current knowledge of DV dependencies of normal tissue complications from external beam radiotherapy, and where possible, give quantitative guidance for clinical treatment planning and optimization. Following an initial meeting in October 2007 attended by approximately 75 radiation oncologists, medical physicists, and biostatisticians, extensive literature reviews were undertaken and clinically significant endpoints identified for some 16 organs. Where possible, results were synthesized and compared, guided by the quality and levels of evidence of the studies. Criteria included prospective or retrospective nature, statistical power, presence and reliability of quantitative data on DV effects. Other clinical factors influencing complications were assessed, such as the influence of chemotherapy, fraction size, and preexisting medical conditions. Where available, NTCP model parameters were compiled. This information is expected to provide a boost for further deployment of biological models in the clinical treatment planning process. The results of QUANTEC analyses were published (QUANTEC, 2010). The QUANTEC publications are available on the AAPM website (<http://www.aapm.org>).

### **III. USES OF BIOLOGICALLY RELATED MODELS IN TREATMENT PLANNING**

Dose-response models for tumor and normal structures, as reviewed in section II, can be broadly characterized as either mechanistic or phenomenological. The former attempt to mathematically formulate the underlying biological processes, whereas the latter simply intend to fit the available data empirically. Mechanistic models are often considered preferable, as they may be more rigorous and scientifically sound. However, the underlying biological processes for most tumor and normal tissue responses are fairly complex and often are not fully understood, and it may not be feasible to accurately and/or completely describe these phenomena mathematically. On the other hand, phenomenological models are advantageous since they typically are relatively simple compared to the mechanistic models. Their use obviates the need to fully understand the underlying biological phenomena. Limitations of such empirical approaches are that they strive for mathematical simplicity and thus are limited in their ability to consider more complex phenomena. Further, it may be somewhat risky to extrapolate model predictions beyond the realm within which the model and parameter values were validated. A mechanistic model might be more forgiving in its ability to extrapolate to these more uncertain areas.

As described later in section IV, phenomenological models are mostly used in the currently available BBTPS due to their simplicity in implementation. It is a vision of this task group that more mechanistic models will be employed as BBTPS advances (section VI). In this early stage of BBTPS, the EUD is the most commonly used phenomenological model. As demonstrated with EUD models, this report describes general strategies, advantages, and limitations for using biologically based models for treatment planning.

Biologically related figures of merit may be used for both plan optimization and evaluation. Both tasks are closely related as any optimization algorithm continuously evaluates treatment plans and alters them incrementally in order to improve their figures of merit. However, desired properties (e.g., predicting power) of biological models may differ whether they are used for



plan optimization or plan evaluation. As pointed out by Choi and Deasy (2002), treatment optimization only requires a model to have the ability to steer the optimization process in the desired direction. In contrast, for an effective use of dose-response models in plan evaluation, especially when absolute TCP/NTCP values are used to guide clinical decisions, the accuracy of model predictions is of paramount importance.

### **III.A. BIOLOGICAL MODELS IN PLAN OPTIMIZATION**

#### **III.A.1. Advantages of Biological Cost Functions over DV Cost Functions**

Limitations on use of DV constraints in treatment planning were discussed in section I.B. Optimization criteria based on biologically related models are potentially more versatile and directly associated with treatment outcome than those based on DV criteria.

If biologically related models are constructed to capture the dose response, they would allow some extrapolation beyond the range of clinical evidence. Unfortunately, there is no guarantee that a biologically related model does indeed estimate the consequence of dose distributions if they deviate greatly from the baseline dataset that led to the model parameters. However, for the purpose of dose optimization it is sufficient that the use of the model can guide the optimization towards favorable dose distributions.

Another aspect of plan optimization is that the figure of merit has to address the inevitable variability of patient geometries and resultant dose distributions in a population. In this regard multiple DV criteria for a single organ may become problematic as they need to be given an individual priority and ideally ought to be combined into a single figure of merit to avoid ambiguities. In contrast, biologically related models have the potential to provide an inherent prioritization of multiple DV criteria incorporated in a single figure of merit. The single parameter for organ dose optimization when gEUD is used has been demonstrated by Wu et al. (2003) for head and neck and prostate sites and by Mihailidis et al. (2010) for breast and chest wall sites.

The optimization with cost functions based on the EUD concept, commonly used in the available BBTPSs, is straightforward and numerically expedient (Romeijn et al. 2004; Alber and Reemtsen 2007).

#### **III.A.2. Precautions for Using Biological Models in Plan Optimization**

As most of the currently available BBTPSs use EUD/gEUD-based optimizations, we mainly discuss the concerns with EUD here. With respect to optimization, the DV effect incorporated by a EUD-based model is of paramount importance. For example, the assumption that a normal tissue responds in serial manner leads to lack of control over the low- and mid-dose range, as the risk of complications is predominantly determined by the high doses. Conversely, if a parallel behavior is assumed, hot spots are allowed but large volumes to lower doses are undesirable. In a worst-case scenario, a serially responding complication would be assumed to behave in a parallel fashion. Plan optimization may then be steered towards allowing clinically unacceptable hot spots. If in doubt, one should always maneuver intentionally towards a smaller volume effect, as this will put a limit on both the size and the dose of hot spots in normal tissues during plan optimization.

The gEUD models for serial response do not give rise to local minima of the optimization problem (Choi and Deasy 2002). On the other hand, it cannot be ruled out that gEUD models for parallel response create local minima, though due to their generally less pronounced nonlinearity, this risk is less than that for DV objectives. Although gEUD itself is convex for  $a \geq 1$  (Choi and Deasy 2002), any cost function formulated as a product of nonlinear gEUD/TCP/NTCP models is subject to violating the convex or quasi-convex properties of the underlying biological models (Romeijn et al. 2004). Two examples include the probability of complication-free tumor control,  $P_+$  (Källman et al. 1992a), and the product of sigmoid functions based on gEUD (Wu et al. 2002). Although the clinical significance of local minima remains to be seen (Wu and Mohan 2002), from a mathematical point of view inappropriate choice of the cost function for plan optimization may result in multiple local minima, which diminishes the theoretical advantages of using biological-model-based cost functions.

Direct maximization of biological indices for targets (e.g., TCP or gEUD) is known to produce highly inhomogeneous target dose distributions (de Gersem et al. 1999; Wu et al. 2002) because TCP is increased by the creation of hot spots and using TCP alone does not penalize hot spots. Thus, one must consider limiting planning target volume (PTV) dose inhomogeneity or at least constraining the hot spots to the gross tumor volume (GTV) or clinical target volume (CTV). This can be achieved by adding physical maximum-dose cost functions to optimization criteria for target volumes. Alternatively, the hot spots in target volumes can be controlled using biological cost functions assuming serial response by treating the targets as both tumors and “hypothetical” normal tissues (Wu et al. 2002).

Another challenging issue is to use a biologically related model for a fractionation scheme that is very different from the scheme under which the model was derived. Applying model parameters that were derived for a conventional fractionation scheme to the optimization of a hypofractionated treatment (e.g., stereotactic radiosurgery [SRS] or SBRT) is especially hazardous. In the absence of clinical data to provide guidance, this task group advises adjusting parameters (DV or biological) to steer critical organ doses into a dose volume zone that is proven to be safe clinically. Examples of such safety zones are provided in the reports from the recent QUANTEC initiative (QUANTEC 2010) and from the TG-101 report (Benedict et al. 2010).

### III.A.3. Strategies for Effective Use of Biological Models in Plan Optimization

For plan optimization using biologically related models, two rival, yet complementary, concepts are the EUD and TCP/NTCP models. In one sense, the difference between EUD-based models and TCP/NTCP models is irrelevant, because every TCP/NTCP model can be converted into an EUD model (find the dose which results in the equivalent probability if applied to the whole volume) and vice versa (choose a suitable sigmoid wrapper function which maps EUD onto the interval  $[0, 1]$ ). Note that this EUD does not need to be the same simple expression as the “gEUD.” Thus, TCP/NTCP models are not essential and a EUD-based formalism represents the most basic form of expressing a biologically related cost function for plan optimization (Romeijn et al. 2004; Alber and Reemtsen 2007).

To optimize a plan based on biological models, multiple EUD-dependent goals can be combined to a weighted combination that defines the composite cost function for the optimization algorithm. These biologically related goals usually need to be supplemented by any number of

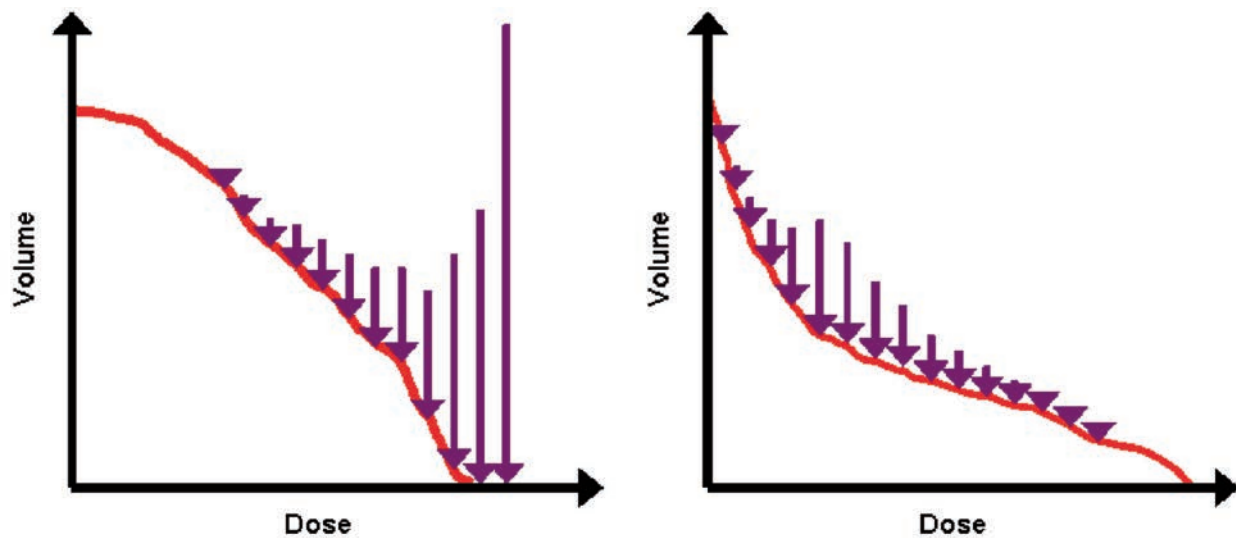


physical goals that would ensure certain properties deemed clinically desirable by a treating physician. For example, a limit on hot spots in the target volume is usually motivated by established clinical practice rather than rigorous biological considerations. Furthermore, there may be biological goals in normal tissues for which no dose-response model exists, for example the overall conformity of the dose to the target volume. All of these cost functions can be combined in optimization, although how this is implemented is determined by the TPS.

It can be beneficial to treat EUD-based cost functions as hard constraints because they are directly associated with control/complication risks. On the other hand, the definition of EUD allows for a certain freedom in shaping the dose distribution. Therefore, EUD constraints are less restrictive than multiple DV constraints and offer an inherent trade-off between different dose levels, allowing controlled violations for some DV constraints while overfulfilling other constraints to generate an overall better dose distribution.

Although each biologically motivated cost function incorporates a specific volume effect and thus favors a certain shape of the dose distribution, the result of an optimization depends on a complex interplay of all participating terms of the cost functions. For this reason, it is essential that the treatment planner understand which traits of a dose distribution are controlled by the chosen cost function terms and which traits are merely coincidental. It is helpful to visualize the action of an EUD-based model on a DVH as a set of connected DV objectives whose weight grows in a specific fashion. For a cost function term assuming serial response, the weight of these virtual DV objectives grows with dose [Figure 1(a)]. The smaller the volume effect, the more rapidly the weight of these objectives grows. For a cost function term assuming parallel response, their weight should tend to zero for very high doses and reach a maximum around the mid-dose range [Figure 1(b)].

The best measure against the hazards of using biologically motivated cost functions is to understand their effect on the dose distribution and to know the desirable properties of the final



**Figure 1.** Weights of “virtual” DV objectives representing the same volume effect as a serial-type cost function (a) or a parallel-type cost function (b).

dose distribution. The overall dose distribution derived from such an optimization should be carefully inspected; one should not rely purely on DVH metrics. Each desired goal should be reflected by a specific cost function term, which should be chosen to be capable of controlling this particular property of the dose distribution sufficiently. Thus, the task of setting up a biologically related optimization problem becomes, in the order of increasing importance: (1) choice of sufficient cost functions; (2) choice of right types of cost functions; (3) choice of right volume effect parameters; and (4) clear idea of what features make a dose distribution acceptable or unacceptable in your clinic. For example, an organ like spinal cord, for which the maximum dose is considered to have the highest priority, is ideally modeled by gEUD with  $a \gg 1$ . This kind of model is very sensitive to high doses while it is very insensitive to low and intermediate doses. Clearly, this kind of behavior is not sought for organs like lung, where the primary objective is to spare sufficient lung volume from intermediate doses while controlling the maximum dose is only of secondary importance. Here, a gEUD model with a smaller  $a$  value or a parallel complication model is a better choice, but one has to be aware that this type of model does not control the maximum dose. In order to achieve this, it needs to be complemented with either a second gEUD model with a greater parameter  $a$  value or a maximum dose constraint. Notice that, in this example, the two models represent two types of complication control with different volume dependency: one aiming to control volume-related complications like pneumonitis and loss of lung function, while the other trying to manage more local complications like destruction of large blood vessels or even necrosis.

#### **III.A.4. Effects of DVH Computation Inaccuracies and Statistical Uncertainties on Plan Optimization Using Biological Models**

Biologically based models that use more pronounced nonlinear functions than DV functions tend to amplify the effects of any uncertainty in the dose and/or DVH computation. For example, the EUD can be calculated directly from the DVH. Depending on the implementation of the TPS, a DVH may be more than just the straightforward statistics of the voxel doses of an organ. Thus, EUD computed directly from the dose calculation grid and from the DVH may differ. Further, all issues associated with the computation of a DVH, such as voxelization, interpolation, binning, and volume normalization, affect the computation of EUD. If the uncertainties are random and not systematic in nature, the EUD error will usually tend to be on the safe side, i.e., normal tissue EUD will be overestimated while target EUD will be underestimated. This is a consequence of the positive curvature of the most common EUD implementations (with the exception of the gEUD for parallel complications). These TPS-related sources of error can be taken into account in practice, if a number of treatment plans that were considered safe are retrospectively evaluated with the EUD models intended for future dose optimization.

A special case of EUD estimate bias arises if the dose distribution is calculated with Monte Carlo methods. Here, the statistical uncertainty of the dose translates into a systematic error of EUD (Kawrakow 2004), which grows with the magnitude of the noise in the dose. For low statistical uncertainties (total dose  $\leq 1\%$ ) this error can be corrected precisely. EUD calculated without this correction from a Monte Carlo dose grid may differ from the values based on DVH. Therefore, low statistical uncertainties, preferably  $<1\%$  of the total dose, are desirable in the Monte Carlo-calculated dose distribution.

### III.B. BIOLOGICAL MODELS IN PLAN EVALUATION

#### III.B.1. Advantages of Biological Models over DV Evaluation Criteria

As with plan optimization, either EUD or TCP/NTCP models can be used for biologically based plan evaluation. Although both concepts can be used interchangeably for plan optimization, the EUD has the advantage of fewer model parameters, as compared to TCP/NTCP models (sections II, III.A.3) and allows more clinical flexibility. The proper calibration of a TCP/NTCP model requires monitoring the outcomes for a large number of patients. In contrast, EUD models can rank a number of treatment plans without having to quantify the actual tumor response/complication risk as long as the chosen parameters ( $\alpha$  in the case of gEUD) are calibrated to give reasonable results for clinical plans for which the treatment outcomes are known. An EUD model can be calibrated against the past clinical practice of any institution simply by calculating the previously applied distribution of EUD values. This establishes a reference range of EUD values that were considered acceptable in the past. Studies along this line have been reported (for example, Wang and Li 2003; Mihailidis et al. 2010).

Thus a properly calibrated EUD model has the potential to provide a reliable ranking of rival plans and is most useful when a clinician needs to select the best plan from two or more alternatives. Of course, it is essential that the clinician understands the prior calibration process and is willing to consider biological evaluation. The utility of EUD for evaluating a single plan is limited. In contrast, properly calibrated TCP/NTCP models can provide direct estimates of outcome probabilities, which are more clinically meaningful than the EUD. If these estimates are within the clinician's goals, the treatment plan under consideration can be accepted without having to explore other possible plans. The disadvantage of TCP/NTCP models is that they require more parameters (most commonly three) and more effort for their calibration as compared to the EUD (one parameter for gEUD [Eq. (1)] and the simplest form of cEUD [Eq. (A1)]). Similar to an EUD model but with more importance, a TCP/NTCP model derived from the experience of other institutions (different TPS, dose calculation, patient population, dose fractionation, etc.) must be applied with extreme caution.

Use of DV criteria (or EUD alone) for plan evaluation implies a binary outcome, i.e., an effect occurs if a DVH passes above a certain point in DV space, and does not occur in the DVH passes below. Such threshold-like behavior of tumor control/complication risk is a rough approximation of actual biological processes. In contrast, biological evaluation metrics in the form of TCP/NTCP provide continuous estimates of outcome probabilities. Also, consider a case when multiple DV points are used to evaluate a dose distribution in a particular organ. It might happen that the dose distribution passes the evaluation test for some points and fails for others, requiring the treatment planner/radiation oncologist to prioritize different DV criteria. Biological metrics may be advantageous in such situations because they can weigh various DV criteria and can condense them into a single unambiguous estimate of biological outcome, as demonstrated by Wu et al (2003).

Some mechanistic biological models [e.g., Eq. (B1)] directly incorporate terms describing radiosensitivity as a function of dose per fraction. If properly calibrated using the data clinically approved for a range of fraction sizes, these models implicitly take into account the dose per fraction effects and can be used to predict outcomes of different fractionation schemes. DV criteria, on the other hand, apply to a single fraction size for which their efficacy has been tested.

If the standard fractionation scheme is significantly altered, DV-based prescription/normal tissue constraints need to be explicitly modified based on clinical experience and/or isoeffect calculations (section II.C).

### **III.B.2. Precautions for Using Biological Models in Plan Evaluation**

In contrast to the use of biological models in plan optimization, where biologically based cost functions are only required to capture the correct volume effect and to steer dose distributions in a desired direction, the use of biological models to replace DV criteria in plan evaluation requires clinically realistic correct plan ranking and/or outcome estimates. To evaluate a particular plan (not just plan ranking), accurate TCP/NTCP models and parameter estimates become absolutely essential. It is also essential that the models used be applied retrospectively to make sure that they agree with the treatments that you know to be safe and effective in your practice. Whether the problem lies in the abstract model or its implementation in TPS, such a reality check is necessary before using a model for clinical plan evaluation. As it is desirable to incorporate outcome data in the treatment planning process, two options exist for using biological models in plan evaluation. The users can derive TCP/NTCP model parameters based on their own experience by calibrating selected model(s) against observed clinical outcomes. This approach has the potential to yield the most reliable data directly reflecting the practice adopted at a particular institution. Furthermore, initial parameter estimates can be easily refined as additional follow-up data become available. However this method may not be feasible for many small and even mid-sized institutions, as it requires expertise in outcome modeling, sufficient patient throughput, and substantial time commitment.

Another option is to cautiously use published parameter values. Published data are available for many tumor sites and complication types (sections II.E and II.G), affording the user a variety of choices. However, this approach is fraught with significant risks if published parameter sets are applied injudiciously without following the same practices that were used to generate the original data (e.g., Ten Haken et al. 2006). Caution should be exercised if clinical and demographic characteristics of the patient population under evaluation differ substantially from those in the original patient cohort used to derive published parameter estimates. The reason is that additional variables influencing the outcome, which were not present in the original population, may be present in the evaluated patient population (e.g., Koh et al. 2006). When using published parameter estimates for plan evaluation, it has to be carefully verified that they apply to the appropriate endpoints, organ volume definitions, and fractionation schemes.

Most NTCP models do not include explicit description of dose-per-fraction effects in the attempt to minimize the number of parameters. Given this, whether one is using in-house or published data, parameter estimates can only be used to evaluate treatment plans corresponding to a narrow range of doses per fraction similar to the doses per fraction in the original patient population. If the fraction size in a plan under evaluation is very different from that in the dataset used to derive parameter estimates, both sets of data should be normalized to the same dose per fraction, usually using the LQ formalism [Eq. (3)]. If the dose per fraction varies considerably in the patient cohort of which parameter estimates are being derived, it is reasonable to normalize all doses to some standard fractionation scheme. Examples include LKB modeling of liver (Dawson et al. 2002) and lung (Seppenwoolde et al. 2003) complications. These sets of

parameter estimates, obviously, work best for fraction-size corrected normal tissue DVHs. However, if these parameter values are used for non-corrected dose delivered with a conventional target fraction size (i.e., ~2 Gy per fraction), the fraction sizes for normal tissues are much less than 2 Gy and hence a model produces conservative overestimates of NTCP. This argument is reversed for hypofractionated delivery, and the model can significantly underestimate the risk of a complication (Xu et al. 2006). Even if the prescription fraction size is unchanged, the simultaneous use of an increasing number of beams/orientations (e.g. with multi-field IMRT) reduces the dose per fraction in the exposed normal tissues away from the target, compared to what they would have seen with a “conventional” plan with a limited number of beam orientations used sequentially (e.g., AP/PA beams followed by opposed oblique beams).

Whether self-derived or published parameter estimates are used, it is essential to standardize the organ volume relative to which the parameter is computed. For example, the EUD or NTCP for rectum and rectal wall will differ because the dose distributions in each volume differ. The EUD or NTCP will also depend on the delineated length of rectum or rectal wall. Much more subtle is the computation of biological indices for the spinal cord, where either a standardized length has to be segmented (e.g., including all thoracic and cervical vertebrae) or the parameter is computed relative to a normalized volume. Care should be taken that for parallel organs, whose response is correlated with the mean dose, the entire organ is included in the image set and dose calculation grid.

Parameter estimates clearly should be used only with the model for which they were derived. In some cases, fits to more than one model are available for the same dataset. For such situations, it has been observed that different NTCP models often provide different answers to important clinical problems (Zaider and Amols 1998; Moiseenko et al. 2000; Muren et al. 2001). It is generally not possible to determine which model is right based on observing fits to clinical data (Moiseenko et al. 2000). To resolve this situation and to ensure further progress in the use of biological models for plan evaluation, concerted efforts to select the most practical models and to create databases of parameter estimates are urgently needed. Such sets of data (e.g., the QUANTEC initiative, section II.G), being supported by experts in TCP/NTCP modeling, will provide a strong basis for TPS manufacturers to include biologically based evaluation tools in their products.

In general, biological figures of merit for target volumes require much less consideration since their utility for outcome prediction is frequently limited by uncertainties of individual tumor biology. Also, current clinical practice demands homogeneous doses to the PTV, which usually includes a large share of normal tissue, while a TCP figure can only be meaningful for the GTV or CTV. It is important to understand which aspects of a target dose distribution influence the TCP. Various investigators have demonstrated using the Poisson-based model with inter-patient heterogeneity [Eq. (B3)] that even very small cold spots may considerably decrease the TCP, whereas the hot spots only affect the TCP to a great extent if the volume of the hot spot is large (Sanchez-Nieto and Nahum 1999; Tomé and Fowler 2000, 2002).

Available sets of TCP parameter estimates are less consistent than NTCP parameters in the sense that different analyses use somewhat different assumptions when deriving model parameters, e.g., fixed number of clonogens vs. fixed clonogen density, inclusion or exclusion of the time factor, etc. Strictly speaking, it is incorrect to apply parameters derived using one set of



assumptions to even a slightly modified model. This poses difficulties because users wishing to integrate TCP calculations into their plan evaluation routine need to implement not only different models that were used to analyze data for different sites, but also different variations of the same basic model. Large sets of TCP data compiled using uniform criteria are rare [e.g., Okunieff et al. (1995)]. Efforts similar to QUANTEC are needed to summarize TCP data and to derive common sets of parameters for one or two models, which could then be built into commercial TPSs.

Finally, current clinical standards for acceptable treatment plans in external beam RT include certain DV goals that are not readily transcribed using biological metrics, such as target dose uniformity and overall conformity of high-dose regions. These goals should be considered separately when EUD/TCP/NTCP are used for plan evaluation.

## **IV. DESCRIPTION AND COMPARISON OF CURRENTLY AVAILABLE TREATMENT PLANNING SYSTEMS EMPLOYING BIOLOGICAL MODELS**

Three commercially available and most commonly used TPSs that employ biological models have been selected to demonstrate the issues discussed above (section III). These three systems, presented in a chronological order based on their release times, are Monaco<sup>®</sup> V1.0 (CMS/Elekta, Maryland Heights, MO), Pinnacle<sup>®</sup> V8.0h (Philips Medical Systems, Andover, MA), and Eclipse V10.0 (Varian Medical Systems, Palo Alto, CA). Each of these systems uses different models and/or different implementation. Initial experiences for using the Monaco and Pinnacle systems have been reported (Semenenko et al. 2008; Qi et al. 2009). Readers are referred to vendor-provided manuals or training for more detailed descriptions about these systems. Selected system-specific issues are discussed. It should be noted that system upgrades may make some issues discussed below no longer relevant.

### **IV.A. CMS MONACO<sup>®</sup>**

At the time this reported is written, the Monaco system (V1.0) does not offer a plan evaluation tool based on biological metrics. Only the plan optimization is discussed for this system.

#### **IV.A.1. Plan Optimization Tools**

The Monaco system is one of the first commercial IMRT treatment planning systems incorporating biologically based optimization features. Monaco offers three biological cost functions titled *Poisson statistics cell kill model*, *Serial complication model*, and *Parallel complication model* to handle dose prescription for targets and OARs exhibiting serial and parallel behavior. Five physical cost functions are also supplied: Quadratic overdose penalty, Quadratic underdose penalty, Overdose DVH constraint, Underdose DVH constraint, and Maximum dose constraint. Despite the presence of conventional DV-based cost functions, the system has been specifically designed to utilize biological models, and produces better plans when the biological optimization features are used to their full potential. The Poisson cell kill model has been made a mandatory cost function for targets. If there is a sole PTV, this function must be assigned to the PTV; addi-

tional physical cost functions may also be specified. In case of multiple PTVs, the Poisson cell kill model must be used to create optimization criteria for at least one of the PTVs.

The biological cost functions implemented in Monaco are based on a formalism developed at the University of Tübingen (Alber and Nüsslin 1999; Alber 2000). For each of the three functions, a 3D dose distribution in a structure is reduced to a single index that reflects a putative biological response of the structure to radiation. This index is referred to as *isoeffect*. For the Poisson cell kill model and Serial complication model, the isoeffect is expressed in units of dose. For the Parallel complication model, the isoeffect is a percentage of the organ that is damaged. Dose or percentage levels specified by the user as optimization goals are referred to as *isoconstraints*. Following each iteration, isoeffects are recomputed and compared with isoconstraints to determine whether user-specified criteria have been met.

Isoeffects for targets (i.e., the Poisson cell kill model) are calculated as

$$D_{eff} = -\frac{1}{\alpha'} \ln \left[ \frac{1}{\rho' V} \int_V f(D(\vec{x})) dx^3 \right], \quad (17)$$

where  $\alpha'$  is the average cell sensitivity,  $\rho'$  is the average clonogen density,  $V$  is the total volume of the organ (i.e., number of voxels), and  $f(D(\vec{x}))$  is a biological response function given by

$$f(D(\vec{x})) = \rho(\vec{x}) \exp[-\alpha(\vec{x})D(\vec{x})], \quad (18)$$

where  $\rho(\vec{x})$  is the local density of clonogenic tumor cells,  $\alpha(\vec{x})$  is the cell sensitivity in a particular voxel, and  $D(\vec{x})$  is the absorbed dose in this voxel. Equations (17) and (18) are ready to accommodate information about spatially heterogeneous clonogen density and/or clonogen radiosensitivity that will become available in the future, pending advances in biological imaging techniques. However at present, spatial variations in either clonogen density or cell sensitivity are not taken into account, i.e.,  $\rho(\vec{x}) \equiv \rho'$  and  $\alpha(\vec{x}) \equiv \alpha'$ . Parameter  $\rho'$  has been hard-coded to  $10^6$  clonogens per voxel and presently its value has no impact on isoeffect calculations because  $\rho(\vec{x})$  in Eq. (18) and  $\rho'$  in Eq. (17) cancel out. Parameter  $\alpha'$  takes on user-specified values in the range 0.1 to 1.0 Gy<sup>-1</sup> with a default value of 0.25 Gy<sup>-1</sup>. Equation (18) represents a simplified (only linear component of cell killing is taken into account) expression for the number of surviving clonogens in a voxel based on the standard Poisson statistics-based TCP model [Eq. (B1)]. Equation (17) is an inverted form of Eq. (18) and conceptually represents the equivalent uniform dose (section II.A).

Isoeffects for serial-type OARs are specified in terms of an effective dose given by

$$D_{eff} = \left[ \frac{1}{V} \int_V g(D(\vec{x})) dx^3 \right]^{1/k}, \quad (19)$$

where  $k$  is the volume effect parameter,  $V$  is the total number of voxels, and a response function applied to each voxel takes the form

$$g(D(\vec{x})) = [D(\vec{x})]^k. \quad (20)$$

Combination of Eqs. (19) and (20) is mathematically equivalent to the gEUD formula (section II.A) with  $k \equiv a$ .  $D_{eff}$  approaches maximum dose as  $k$  increases.

Although the Serial complication model with  $k = 1$  may be used to handle situations when mean organ dose needs to be controlled, i.e., for parallel-type structures, Monaco provides an additional cost function for this purpose. Isoeffects for the Parallel complication model are computed in terms of the mean organ damage:

$$v_{eff} = 100\% \times \frac{1}{V} \int_V h(D(\vec{x})) dx^3, \quad (21)$$

where  $V$  is the total number of voxels and a voxel response function  $h$  is calculated as

$$h(D(\vec{x})) = \left[ 1 + \left( \frac{d_0}{D(\vec{x})} \right)^k \right]^{-1}, \quad (22)$$

where  $d_0$  is referred to as the reference dose, i.e., a dose that results in 50% complication rate,  $k$  is the power-law exponent, which determines the steepness of the sigmoid curve described by Eq. (22). As a rule of thumb, one may choose  $k = 0.15 \text{ Gy}^{-1} \times d_0$  (Alber and Belka 2006). When expressed as a fraction rather than a percentage, the mean organ damage is mathematically equivalent to the  $f_{dam}$  concept of the parallel complication model (appendix C). Properties of biological cost functions employed in Monaco are summarized in Table I. Limits imposed on parameter or isoconstraint values are shown in parentheses. Because the Poisson cell kill model does not include a mechanism to control hot spots in target volumes, a physical cost function, either the Quadratic overdose penalty or Maximum dose, must be added to create optimization goals for target volumes. In our practice, it has always been possible to design good quality treatment plans using the three biological functions listed in Table I and the Quadratic overdose penalty cost function (Semenenko et al. 2008).

**Table I.** Biological Models Used for Treatment Plan Optimization in CMS Monaco.

Structure Type	Name	Parameters	Objectives/ Constraints	Comments
Target	Poisson statistics cell kill model	Cell sensitivity (0.1–1.0 Gy <sup>-1</sup> )	Prescription (1–150 Gy)	Mandatory cost function for targets; no penalty for hot spots
OAR	Serial complication model	Power-law exponent (1–20)	Equivalent uniform dose (1–150 Gy)	Effective for controlling maximum organ dose
OAR	Parallel complication model	Reference dose (1–100 Gy) Power-law exponent (1–4)	Mean organ damage (1%–100%)	Effective for controlling mean organ dose

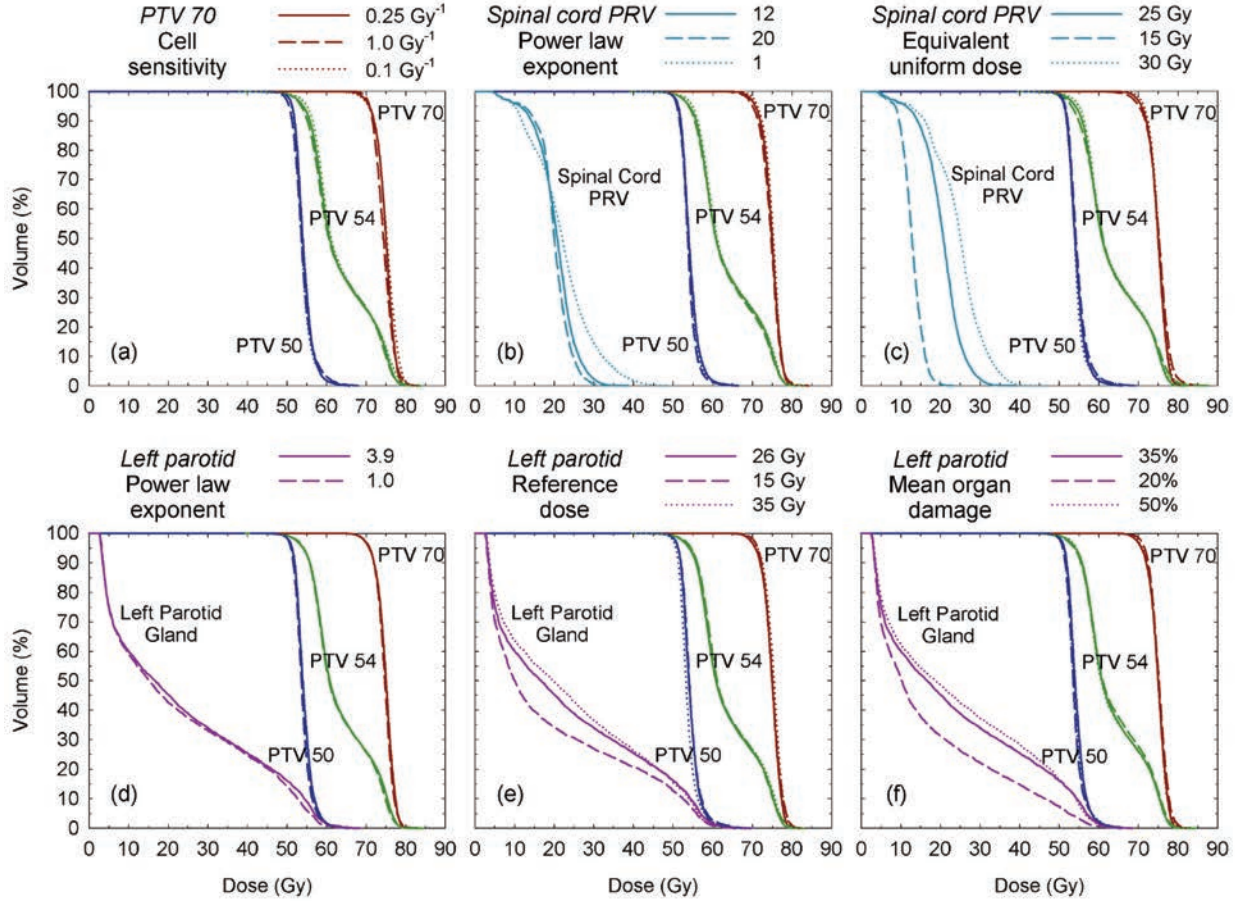


Monaco supports the concept of constrained optimization. That is, the two biological cost functions used for OARs and all physical cost functions are treated as hard constraints. All optimization criteria specified using these cost functions will be met by the TPS. The Poisson cell kill model is only an objective, meaning that the system finds the optimal cell kill subject to satisfying the hard constraints. As a result, the treatment planner does not have to specify any weights, i.e., effectively all cost functions except the Poisson cell kill model are assigned infinitely large weights. Because target dose is only an objective, achieving this objective may often be limited by one or more constraints on dose in nearby OARs or constraints on hot spots in target volumes. A Sensitivity Analysis tool (Alber et al. 2002) is provided to help the planner to identify the limiting constraints. Desired target coverage could then be obtained by relaxing (increasing) isoconstraint values for the restrictive cost functions.

In addition to primary biological constraints for OARs (i.e., Serial and Parallel complication models), Monaco allows specification of secondary optimization objectives with these functions. This is referred to as the “Multicriterial option.” This option could be used to attempt to further reduce OAR doses when adequate target coverage had already been achieved or in special cases when additional OAR sparing is more important than adequate target coverage, such as re-treatments for recurrent tumors.

#### IV.A.2. Parameter Sensitivity

The impact of changing Monaco parameters/isoconstraints (Table I) on optimized dose distributions is demonstrated using a test head & neck (hypopharynx) case planned with a 6 MV seven-field IMRT (Figure 2). Only one parameter or isoconstraint at a time was changed. Figure 2(a) shows the result of changing cell sensitivity for PTV 70 from the default value of  $0.25 \text{ Gy}^{-1}$  to maximum and minimum allowable values of  $1.0$  and  $0.1 \text{ Gy}^{-1}$ , respectively. This parameter has a small effect on minimum dose in PTV 70, with greater values of cell sensitivity corresponding to larger minimum doses:  $60.4 \text{ Gy}$  for cell sensitivity of  $0.1 \text{ Gy}^{-1}$ ,  $62.5 \text{ Gy}$  for  $0.25 \text{ Gy}^{-1}$ , and  $65.7 \text{ Gy}$  for  $1.0 \text{ Gy}^{-1}$ . Because the Poisson cell kill model is only an objective, changing prescription dose for PTV 70 without any changes in dose-limiting constraints does not affect target DVHs (data not shown). Behavior of the Serial complication model has been investigated on an example of spinal cord planning organ-at-risk volume (PRV), which was defined as 5-mm expansion around the spinal canal. Increasing power-law exponent parameter or decreasing EUD isoconstraint for the Serial complication model applied to the spinal cord PRV results in lower maximum doses for the cord accompanied by some deterioration in target coverage [Figures 2(b) and 2(c), dashed lines], and vice versa [Figures 2(b) and 2(c), dotted lines]. Changing power-law exponent parameter for the Parallel complication model applied to the parotid gland from a 3.9 value suggested in Monaco reference documentation to the lowest allowed value of 1.0 [Figure 2(d)] does not result in any discernable trend. Smaller reference dose [Figure 2(e)] or mean organ damage [Figure 2(f)] values in the Parallel complication model lead to lower mean doses to the parotid gland. In the example chosen, reducing the reference dose or mean organ damage for the left parotid gland results in substantial sparing of that gland with no deterioration of target coverage. However, mean dose to the other parotid gland somewhat increases (not shown).



**Figure 2.** Sensitivity of dose distributions obtained with CMS Monaco to changes in parameters or iso-constraints. Solid lines show base plan DVHs; dashed and dotted lines show DVHs obtained by varying each parameter/isoconstraint in either direction from its base value. For clarity, only DVHs for an affected OAR (spinal cord PRV or left parotid gland) and for target volumes (PTV 70, PTV 54, and PTV 50) are shown.

## IV.B. PHILIPS PINNACLE®

### IV.B.1. Plan Optimization Tools

Pinnacle<sup>3</sup> (V8.0h) offers biological optimization features incorporated into its P<sup>3</sup>IMRT inverse treatment planning module. The biological objective functions have been developed by RaySearch Laboratories AB (Stockholm, Sweden) (Hårdemark et al. 2004). As opposed to Monaco, Pinnacle is not a designated biologically based optimization system, but rather uses biological cost functions to enhance the traditional, DV-based optimization approach. In addition to a number of DV cost functions (Min dose, Max dose, Uniform dose, Min DVH, Max DVH, and Uniformity), Pinnacle has at its disposal three biological cost functions denoted Min EUD, Target EUD, and Max EUD. These cost functions are defined as (Hårdemark et al. 2004):

$$F(EUD) = \theta(EUD, EUD_0) \left( \frac{EUD - EUD_0}{EUD_0} \right)^2, \quad (23)$$

where  $EUD_0$  is the desired dose level specified by the user. Actually attained dose,  $EUD$ , is computed according to the gEUD formalism (section II.A). Function  $\theta$  is defined as

$$\theta(EUD, EUD_0) = \begin{cases} H(EUD - EUD_0) & \text{for Max } EUD \\ 1 & \text{for Target } EUD, \\ H(EUD_0 - EUD) & \text{for Min } EUD \end{cases} \quad (24)$$

where  $H$  is the Heaviside step function.

Properties of biological cost functions implemented in Pinnacle for the purpose of plan optimization are summarized in Table II. Each function requires specification of a single volume parameter,  $a$ , which has the same interpretation as described by Niemierko (1999). For negative  $a$  values, cold spots influence  $EUD$  to a greater extent, and for positive  $a$  values,  $EUD$  is most influenced by hot spots. Generally, negative  $a$  values are an appropriate choice for targets, positive  $a$  values should be used for serial structures, and  $a = 1$  should be used for parallel structures. Biophysically meaningful ranges of the volume parameter for a corresponding cost function are shown in parentheses in Table II. However in contrast to Monaco, Pinnacle does not impose any limits on values of the volume parameter or  $EUD$ .

Pinnacle employs the traditional unconstrained optimization approach. Target and OAR cost functions contribute to the overall cost function in proportion to user-specified weights. Also for any cost function (with the exception of the Uniformity, which can only be used as a constraint and the Uniform dose, which can only be used as an objective), a treatment planner has an option to use it as either an objective or constraint. The latter effectively sets a very high penalty for violating an optimization goal specified using this cost function.

Philips Pinnacle allows a gradual transition to biologically based inverse planning through combining conventional DV-based and novel EUD-based cost functions. Especially for targets, it is advised to supplement EUD-based objectives with DV-based ones to better control target dose distributions (Hårdemark et al. 2004; Wu et al. 2003).

**Table II.** Biological Models Used for Treatment Plan Optimization in Philips Pinnacle.

Structure Type	Name	Parameters	Objectives/ Constraints	Comments
Target	Min EUD	Volume parameter ( $a < 1$ )	EUD (Gy or cGy)	Penalizes for too low EUD
Target	Target EUD	Volume parameter ( $a < 1$ )	EUD (Gy or cGy)	Penalizes for any deviation from the desired EUD
OAR	Max EUD	Volume parameter ( $a \geq 1$ )	EUD (Gy or cGy)	Penalizes for too high EUD; can be used with both serial and parallel structures

### IV.B.2. Plan Evaluation Tools

Pinnacle provides two separate tools, titled NTCP/TCP Editor and Biological Response panel, for plan evaluation with the help of biological models. The NTCP/TCP Editor is used to obtain NTCP and TCP estimates. NTCP is calculated according to the LKB model (Eqs. 13–15). A database of model parameters originating from Burman et al. (1991) is available, and a user is given the option to customize parameter values. TCP is calculated using an empirical sigmoid curve corresponding to the CDF of the normal distribution. Users are responsible for specifying their own estimates of two model parameters describing dose to control 50% of tumors,  $D_{50}$ , and a measure of a slope of the sigmoid curve,  $m$ .

Users licensed for Biological Evaluation may take advantage of an enhanced plan evaluation tool that includes a database of endpoint- and tumor stage-specific parameter values (accompanied by literature references) for calculation of NTCP and TCP, capability to compare alternate treatment plans side-by-side, graphical representation of NTCP/TCP for individual structures, and composite estimates of NTCP, TCP, and probability of complication-free tumor control for the entire plan. Models and parameter estimates implemented in the Biological Response panel are based on the expertise collected at the Karolinska Institute and Stockholm University (Lind et al. 1999; Kåver et al. 1999). The Källman  $s$ -model, also known as the relative seriality model [Eq. (16)], is used to calculate NTCP. The Poisson model with LQ cell survival [Eqs. (6)–(8)] is used to describe response of the entire organ to uniform irradiation. TCP is calculated with the Poisson model [Eqs. (5)–(8)]. The majority of default parameter values provided for NTCP calculations come from a Ph.D. thesis (Ågren 1995), which is not readily available in the open literature. Given the publication date, the parameter estimates were likely obtained by refitting the relative seriality model to the Emami et al. (1991) data. Default values of  $D_{50}$  and  $\gamma$  provided for TCP calculations are taken from old literature dating back to the 1960s, with the most recent report being from 1993. Both TCP and NTCP parameter databases are customizable, but the choice of models is fixed. The models used for biological plan evaluation in Philips Pinnacle are summarized in Table III.

### IV.B.3. Parameter Sensitivity

Sensitivity of dose distributions obtained with Pinnacle to changes in volume parameter (same as power-law exponent in Monaco) or EUD (Table II) is shown in Figure 3 for the same head & neck case irradiated with the 6 MV beam. Optimization goals for PTV 70 were created using the Target EUD cost function combined with the Uniformity constraint. Variations in the volume parameter specified with Target EUD cost function have very small effect on PTV 70 DVH [Figure 3(a)]. Minimum dose to PTV 70 slightly increases as the volume parameter decreases: 62.1 Gy for  $a = 50$ , 62.4 Gy for  $a = -10$ , and 64.6 Gy for  $a = -50$ . Increasing the EUD for PTV 70 has an effect of shifting the DVH toward higher doses [Figure 3(b)]. Increasing the volume parameter for the Max EUD cost function applied to the spinal cord PRV from 12 to 20 results in the reduction of maximum dose to the cord and some deterioration of target coverage [Figure 3(c)]. Decreasing the volume parameter from 12 to 1 has little, if any, effect on the dose distributions. Maximum dose to the cord decreases as the EUD value specified for the Max EUD cost function is decreased [Figure 3(d)]. Minimum dose in a PTV closest to the spinal cord PRV (PTV 54 in this example) also decreases in proportion to the EUD for the cord. Similar

**Table III.** Biological Models Used for Treatment Plan Evaluation in Philips Pinnacle.

Tool	Structure Type	Name/Description	Parameters/ Inputs	Comments
NTCP/TCP Editor	Target	Empirical TCP model	$D_{50}, m$	Sigmoid curve represented by the CDF of the normal distribution
	OAR	Lyman-Kutcher model	$D_{50}, m, n$	Database of model parameters is provided
Biological Response Panel	Target	Poisson/LQ-based TCP model	$D_{50}, \gamma, \alpha/\beta$	Database of model parameters is provided
	OAR	Källman $s$ -model	$D_{50}, \gamma, \alpha/\beta, \text{seriality } (s)$	Database of model parameters is provided
	Multiple targets	Composite TCP	TCP for individual targets	$TCP = \prod_i TCP_i$
	Multiple OARs	Composite NTCP	NTCP for individual OARs	$NTCP = 1 - \prod_i (1 - NTCP_i)$
	Targets and OARs	Probability of complication-free tumor control	Composite TCP, composite NTCP	$P_+ = \max(TCP - NTCP, 0)$

trends were observed for the Max EUD cost function applied to the left parotid gland, i.e., increasing the volume parameter or decreasing the EUD reduces dose to the parotid gland and creates cold spots in adjacent target volume (PTV 54). Decreasing the volume parameter or increasing the EUD slightly increases dose to the parotid gland with virtually no effect on target coverage [Figures 3(e) and 3(f)].

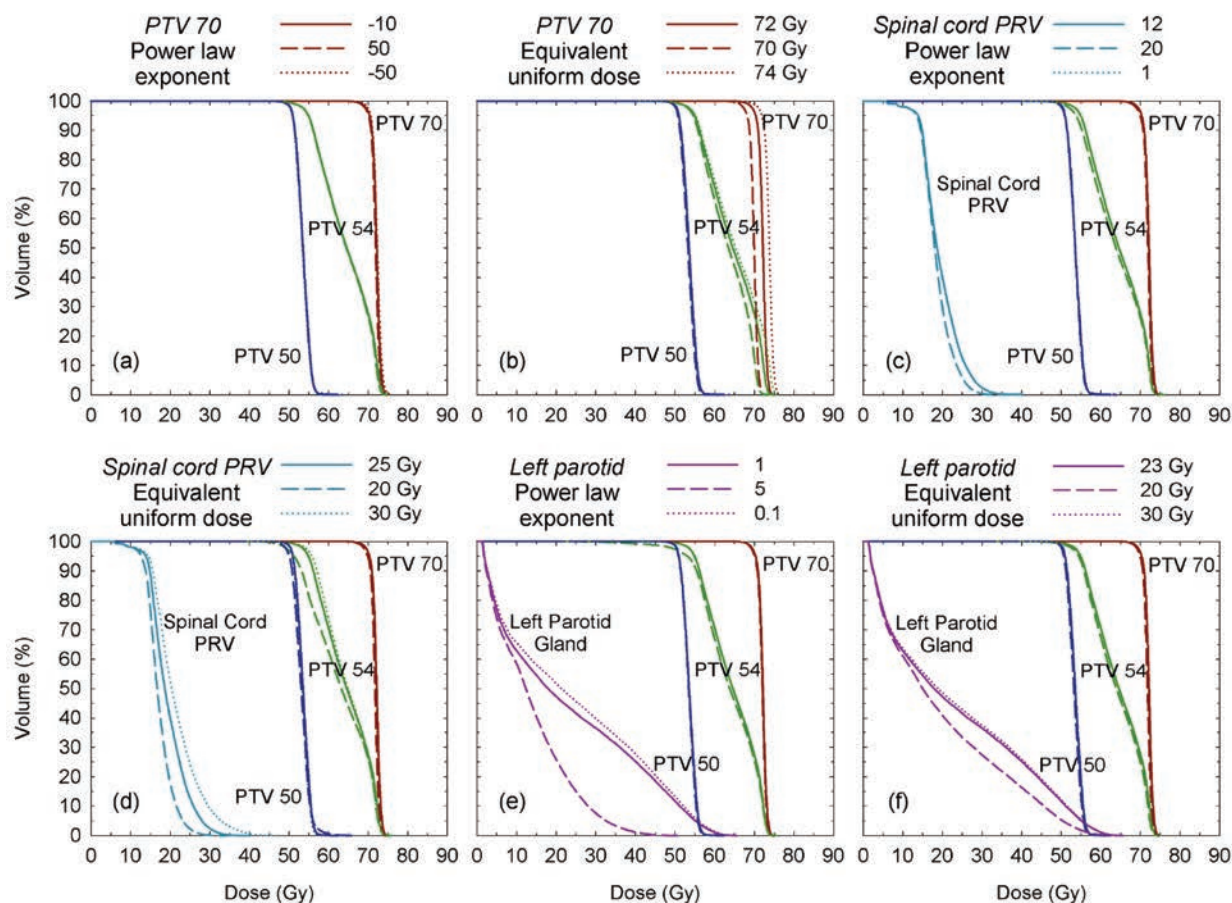
## IV.C. VARIAN ECLIPSE

### IV.C.1. Plan Optimization Tools

Eclipse (V10.0) provides biological optimization through the use of a “plug-in” to an application by RaySearch Laboratories (Stockholm, Sweden). Selecting biological optimization transfers all patient and plan information to the application for fluence optimization with a separate rapid calculation algorithm. The optimized fluences are then returned to the Eclipse dose engine for the final dose calculation.

The optimizer differentiates between biological and physical functions used in the optimization. The biological models used in the optimization include TCP Poisson-LQ, NTCP Poisson-LQ, and NTCP Lyman, and are tabulated in Table IV. The TCP Poisson-LQ and NTCP Poisson-LQ models are identical, respectively, to the TCP and NTCP models implemented in the Biological Response panel in Pinnacle. The NTCP Lyman model is the LKB model calculated based on an LQ-corrected DVH [Eq. (3)]. This model is thus somewhat different from the “Lyman-Kutcher” model in the NTCP/TCP Editor in Pinnacle, which does not take an extra  $\alpha/\beta$





**Figure 3.** Sensitivity of dose distributions obtained with Philips Pinnacle to changes in volume parameter (power-law exponent) or EUD. Solid lines show base plan DVHs; dashed and dotted lines show DVHs obtained by varying each parameter in either direction from its base value. For clarity, only DVHs for an affected OAR (spinal cord or left parotid gland) and for target volumes (PTV 70, PTV 54, and PTV 50) are shown.

parameter and is calculated based on non-corrected DVHs. The models allow specification of repair time for NTCP models and repair/repopulation times for TCP. The biological functions allow the user to specify the weight (Constraint Bound Percentage) used in calculation of the cost function. Physical functions do not allow assignment of a weight but are regarded as constraints that cannot be compromised. Physical functions include: maximum dose, maximum dose for percentage structure volume, maximum gEUD, uniformity. For structures defined as targets one may additionally define minimum values for dose, dose for percentage of structure volume, and gEUD. Each structure may also have a conformity constraint that specifies the dose gradient near to the structure.

A library of tissue-specific parameter values for the TCP and NTCP models is provided, enabling selection of standardized values within the Biological Optimizer application. The library may be edited and modified to include user-specified parameter sets and tissues.

The optimizer screen displays the evolution of items used to monitor and modify parameters used in optimization: optimization functions and parameter values, color wash of coronal and

**Table IV.** Biological Models Used for Treatment Plan Optimization in Varian Eclipse.

Structure Type	Name	Parameters	Objectives/ Constraints	Comments
Target	Min EUD	Volume parameter ( $a$ )	EUD (Gy or cGy)	Penalizes for too low values; cannot be weighted; listed under physical functions
Target or OAR	Max EUD	Volume parameter ( $a$ )	EUD (Gy or cGy)	Penalizes for high values; cannot be weighted; listed under physical functions
Target	TCP Poisson-LQ	$D_{50}$ , $\gamma$ , $\alpha/\beta$ , seriality ( $s$ ), $T_{1/2}$ for short vs. long repair time, % with long repair time, repopulation times: $T_{pot}$ and $T_{start}$	TCP	Penalizes for small values; can be weighted
OAR	NTCP Poisson-LQ	$D_{50}$ , $\gamma$ , $\alpha/\beta$ , seriality ( $s$ ), $T_{1/2}$ for short vs. long repair time, % with long repair time	NTCP	Penalizes for large values; can be weighted
OAR	NTCP Lyman	$D_{50}$ , $m$ , $n$ , $\gamma$ , $\alpha/\beta$ , $T_{1/2}$ for short vs. long repair time, % with long repair time	NTCP	Penalizes for large values of NTCP; can be weighted

sagittal views of the evolving dose distribution, beam fluence patterns, charts and tables of evolving cost function values for each constraint, DVH, and a graph plotting sensitivity of the biological response for a change in dose per fraction for constant total number of fractions. Dose distributions from plans calculated in Eclipse may be specified to be used as a base dose from which the optimization proceeds. During optimization the user iterates through addition and modification of optimization functions to achieve the desired DVH characteristics or until the optimization thresholds are reached.

#### IV.C.2. Plan Evaluation Tools

After a treatment plan has been generated in Eclipse, it may be evaluated using the Biological Evaluation Module. The same biological functions used in the optimizer may be used to calculate

**Table V.** Biological Models Used for Treatment Plan Evaluation in Varian Eclipse.

Tool	Structure Type	Name	Parameters	Comments
Biological Evaluation	Target	TCP Poisson-LQ	$D_{50}$ , $\gamma$ , $\alpha/\beta$ , seriality( $s$ ), $T_{1/2}$ for short vs. long repair time, % with long repair time, repopulation times: $T_{pot}$ and $T_{start}$	User selectable parameters or from database of model parameters
	OAR	NTCP Poisson-LQ	$D_{50}$ , $\gamma$ , $\alpha/\beta$ , seriality( $s$ ), $T_{1/2}$ for short vs. long repair time, % with long repair time	User selectable parameters or from database of model parameters
	OAR	NTCP Lyman	$D_{50}$ , $m$ , $n$ , $\alpha/\beta$ , $T_{1/2}$ for short vs. long repair time, % with long repair time	User selectable parameters or from database of model parameters

NTCP and TCP values for structures. Evaluation of EUD is not supported in this module. Models used for plan evaluation are included in Table V.

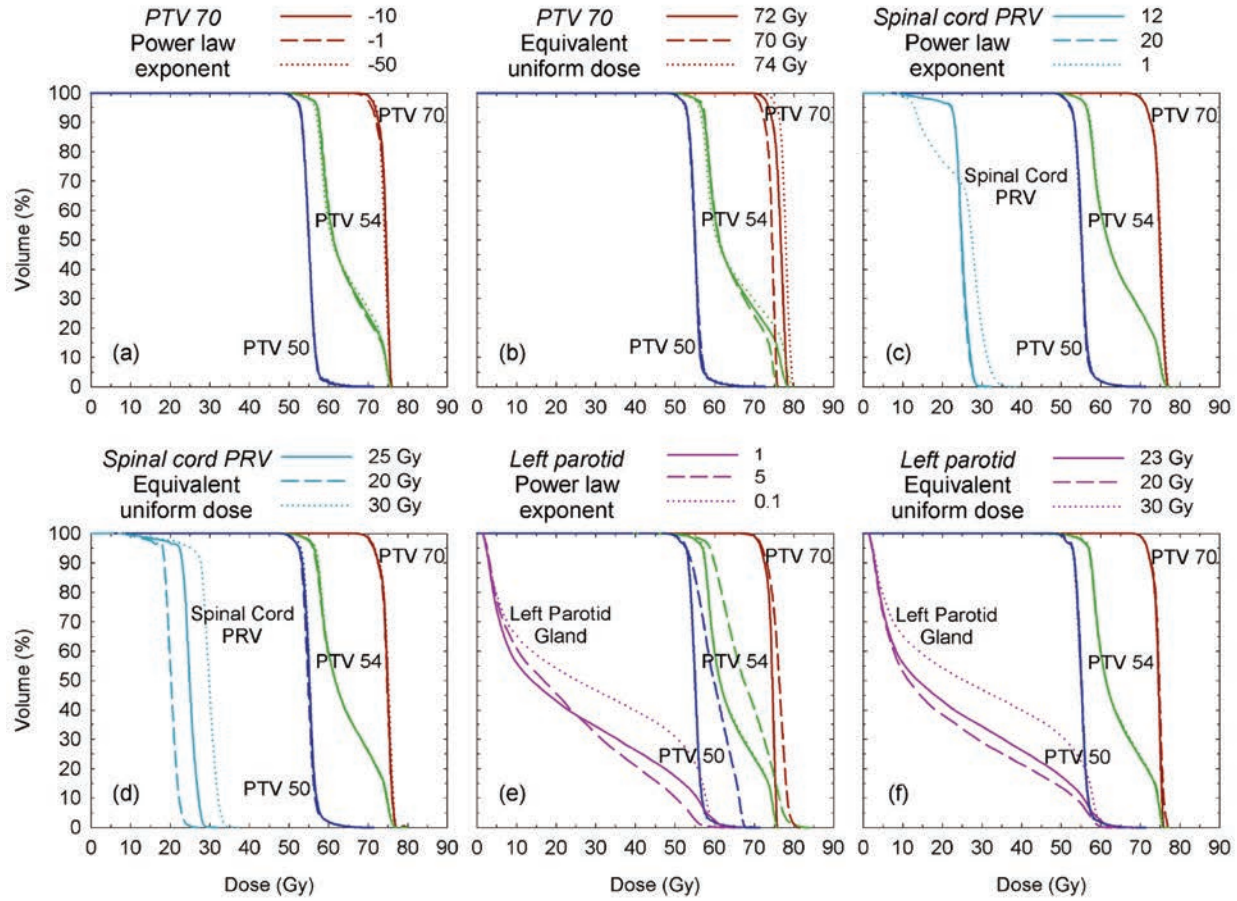
The tool may be used to evaluate effect on NTCP and TCP values of changing fractionation schedules (e.g., twice vs. once per day), changing number of fractions or scaling total dose. In addition to the conventional DVH, two other graphs are available for plan evaluation. The LQ-Scaled DVH utilizes the  $\alpha/\beta$  ratio specified in the NTCP or TCP model to scale the DVH to equivalent values for 2-Gy fractions [Eq. (3)] as a standard benchmark for plan comparison. The Radiobiological Response graph shows the potential effect of altering total plan dose by plotting the value of NTCP or TCP versus a scale factor (0.7 to 3.0) for the total dose.

Since the RaySearch libraries are used in Pinnacle also, the general comments in section IV.B.2 on parameters are applicable to the Eclipse evaluation tools.

### IV.C.3. Parameter Sensitivity

The sensitivity of DVHs to changes in model parameters, e.g., gEUD volume parameter (power-law exponent), or to threshold levels for the gEUD specified in the optimizer, were tested in Eclipse in a similar way as that discussed for Monaco and Pinnacle. Results of these tests are illustrated in Figure 4. Optimization goals for PTV 70 were created with a maximum dose constraint and a minimum EUD constraint, instead of a minimum dose constraint. The maximum dose constraint was selected over the use of a uniformity constraint since it provided more reliably consistent results. If only a gEUD constraint is used, without a max dose or uniformity constraint, then the maximum dose in the PTV 70 volume rose to >100 Gy. This is consistent with the discussion in section III.A.2, on the lack of sensitivity to hot spots for TCP and gEUD optimization constraints for target tissues. In the creation of the data in Figure 4, only one parameter was changed at a time. For example, Figure 4(a) shows the result of changing power-law





**Figure 4.** Sensitivity of dose distributions obtained with Varian Eclipse to changes in volume parameter (power-law exponent) or EUD for elected target and OARs. Solid lines show base plan DVHs; dashed and dotted lines show DVHs obtained by varying a parameter from its base value, for example, (a) changing the power-law exponent for PTV 70 as indicated by the headings. For clarity, only DVHs for an affected OAR (spinal cord or left parotid gland) and for all target volumes (PTV 70, PTV 54, and PTV 50) are shown.

exponent for PTV 70 from the default value of  $-10$  to values of  $-1$  and  $-50$ . It is seen from Figure 4(a) that variations in DVHs for PTV 70, PTV 54, and PTV 50 were relatively insensitive to the magnitude of the volume parameter.  $V_{70}$  was 97.6, 98.5, 99.2, and 99.5% for  $a$  values of  $-1$ ,  $-5$ ,  $-10$ ,  $-50$ , respectively. Figure 4(b) presents the result for varying gEUD for PTV 70 that changes the DVHs for PTV 70 and PTV 54. Figure 4(c) demonstrates that larger values of the power-law exponent ( $a > 10$ ) have similar effects on the DVHs, while the  $D_{50}$  for cord PRV was 28, 25, and 25 Gy for  $a = 1$ , 12, and 20, respectively. Increasing the threshold for maximum gEUD shifted the cord DVH uniformly toward the threshold dose [Figure 4(d)]. Since the parotid abuts the target volumes, interaction of constraint on the normal tissue affecting the target dose was noticeable. Sensitivity to the value of the power-law exponent was significant for DVH of the parotid [Figure 4(e)]. Values of  $V_{45} = 36$ , 22, and 16% for the parotid were obtained for  $a = 0.1$ , 1, and 5, respectively. Mean doses were similar for  $a = 1$  and  $a = 5$ . The significant changes in the DVHs for the target volumes (PTV 70, PTV 54, and PTV 50) were observed

with the large volume parameter value (i.e.,  $a = 5$ ). Fixing the volume parameter at  $a = 1$  for the parotid and then varying the gEUD threshold increase or decrease the mean doses in the expected direction [Figure 4(f)].

Constraints using NTCP and TCP values may also be used to shape the dose distribution. This is more complex owing to the number of input parameters and, in principal, produces similar results to gEUD constraints as outlined in section III.A.3. To obtain a clinically desirable dose distribution using NTCP- and TCP-based cost functions, it is often necessary to use parameters for these functions quite different from those used to evaluate their value. For example using a  $D_{50}$  much lower for optimizing the parotid dose can produce a better final dose distribution than obtained using the same value of  $D_{50}$  used to evaluate the NTCP of the plan.

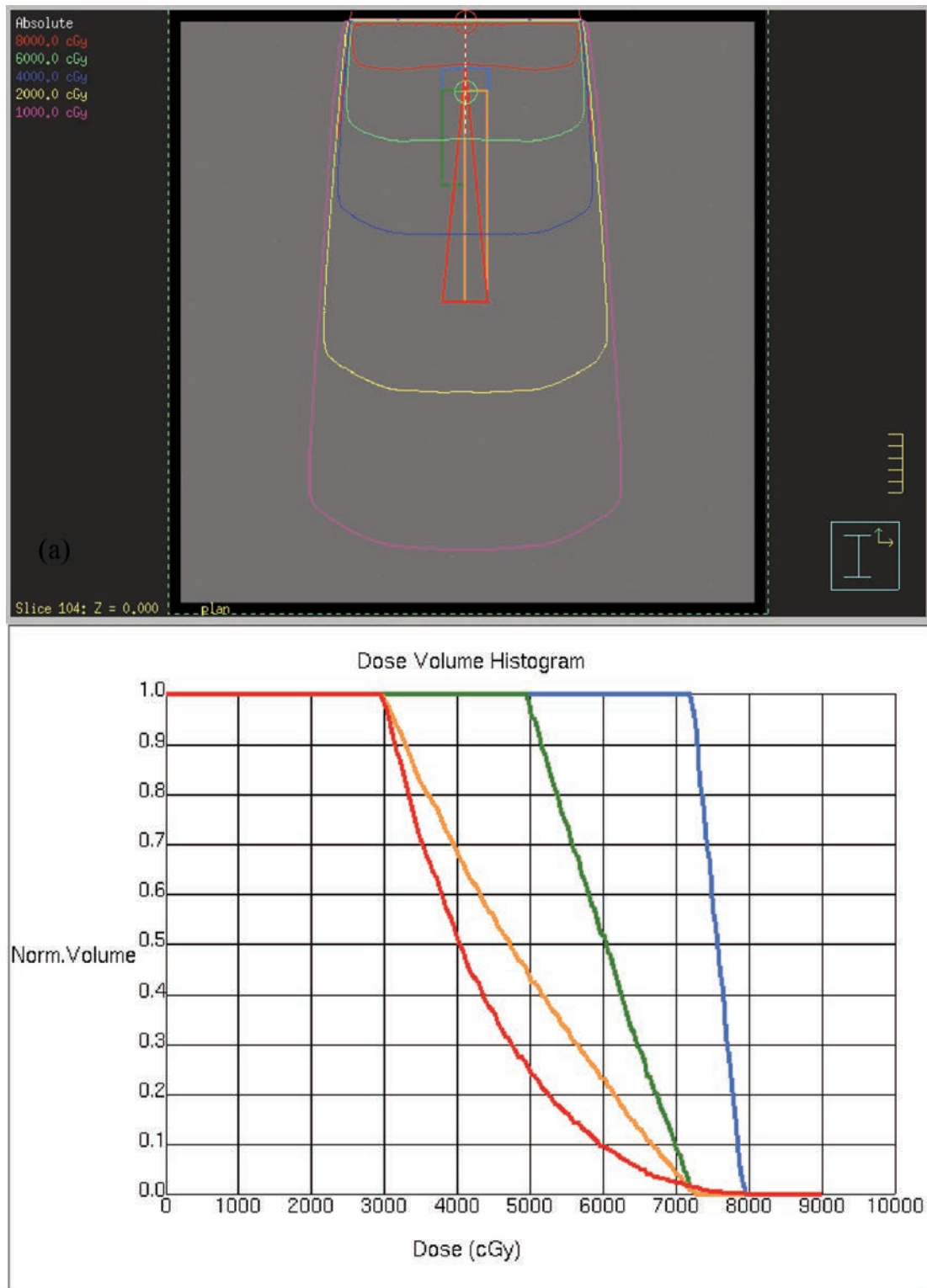
#### **IV.D. COMPARISON OF CMS MONACO, PHILIPS PINNACLE, AND VARIAN ECLIPSE SYSTEMS**

##### **IV.D.1. Comparison and Verification of EUD, NTCP, TCP, or P+ Values Obtained with Pinnacle and Eclipse Systems**

Both Pinnacle and Eclipse systems provide tools to calculate EUD, TCP, NTCP, or P+ (Table III) as plan evaluation metrics. To verify this calculation, selected metrics have been calculated manually and compared to the same quantities reported by Pinnacle and Eclipse. All work in this section has been performed using a benchmark case, which involves a single 6 MV,  $20 \times 20$  cm<sup>2</sup> photon beam incident on a sufficiently large cubical water phantom at 100 cm source-to-surface distance. A dose of 72 Gy in 40 fractions was prescribed to a point at 6 cm depth along the central axis. Four simple structures (3 rectangular, 1 triangular) were created inside the phantom [Figure 5(a)]. The DVHs for these structures look similar to those encountered in a typical plan [Figure 5(b)]. This case was chosen because it could be easily and reproducibly set up in any commercial TPS, providing a simple, nearly identical input dose distribution for comparison of biological evaluation tools between different TPSs. Use of a percentage depth dose (PDD)-based dose distribution and simple structures also facilitates spreadsheet-based, hand calculations of DVH, TCP, and NTCP values for comparison. Details on the geometries of the structures in the benchmark phantom are provided in Table VI.

In a DVH view page of the Pinnacle system, users can specify a value of the volume parameter,  $a$ , for each structure, and the TPS will calculate and report gEUD in the region of interest ROI Statistics section in addition to physical quantities. By default,  $a = 1$ , and the reported gEUD is the same as the mean dose. Parameter  $a$  was varied in the range between  $-50$  and  $50$ , and gEUD values reported by the TPS for all four structures were recorded. The same gEUD values were then calculated on the spreadsheet based on DVHs exported from Pinnacle. Both sets of data agreed very well ( $<0.1\%$ ) for all combinations of the structure and volume parameter.

To spot-check results reported in the Biological Response panel from Pinnacle, TCP calculations were performed for two structures and NTCP calculations were performed for all four structures. Input parameters and calculated values are detailed in Table VII. Model parameters were chosen from the included library so that resulting TCP and NTCP estimates are not equal to 0 or 1. All individual TCP and NTCP values and composite metrics (composite TCP,



**Figure 5.** Benchmark case for verification of EUD, NTCP, TCP, and P+ calculations in Pinnacle. (a) Beam setup and structures. (b) DVHs.

**Table VI.** Details of Benchmark Phantom Structures.

Structure	Dimensions (cm)	X coordinate range (cm)	Y coordinate range (cm)	Depth range (cm)
PTV Rectangle	$4 \times 4 \times 2$	-2 to 2	-2 to 2	4 to 6
Rectangle 1	$2 \times 4 \times 8$	-2 to 0	-2 to 2	6 to 14
Rectangle 2	$2 \times 2 \times 18$	0 to 2	-2 to 2	6 to 24
Triangle 1	$4 \times 4$ (base) $\times 20$	$0 \times 0$ at depth = 4 -2 to 2 at depth = 24	-2 to 2	4 to 24

**Table VII.** TCP and NTCP Values Calculated for DVHs Obtained in the Benchmark Phantom.

Values for TCP and NTCP were calculated using a dose distribution calculated in the Pinnacle system (section IV.D.1). Variability among institutions in reproducing the phantom and differences in 6 MV photon beams will produce small inter-institutional differences in the calculated values.

Structure	PTV Rectangle	Rectangle 1	PTV Rectangle	Rectangle 1	Rectangle 2	Triangle 1
$D_{50}$ (Gy)	63.3	44.2	80	75.1	55.3	46
$\gamma$	5	1.6	3	2.8	3.1	1.8
$\alpha/\beta$ (Gy)	10	10	3	3	3	3
Seriality	N/A	N/A	0.18	8.4	0.69	1
Function	TCP	TCP	NTCP	NTCP	NTCP	NTCP
Value (%)	94.1	80.3	26.6	18.1	23.5	29.5

composite NTCP, and P+) reported by Pinnacle closely matched ( $<0.5\%$ ) the same quantities calculated on the spreadsheet using Eqs. [(5)–(8)] for TCP and Eqs. [(6)–(8), (16)] for NTCP. A close agreement ( $<1.5\%$ ) was also obtained between TCP and NTCP estimates reported by NTCP/TCP Editor (another tool in Pinnacle) and corresponding quantities calculated from the DVHs using Eqs. (13)–(15).

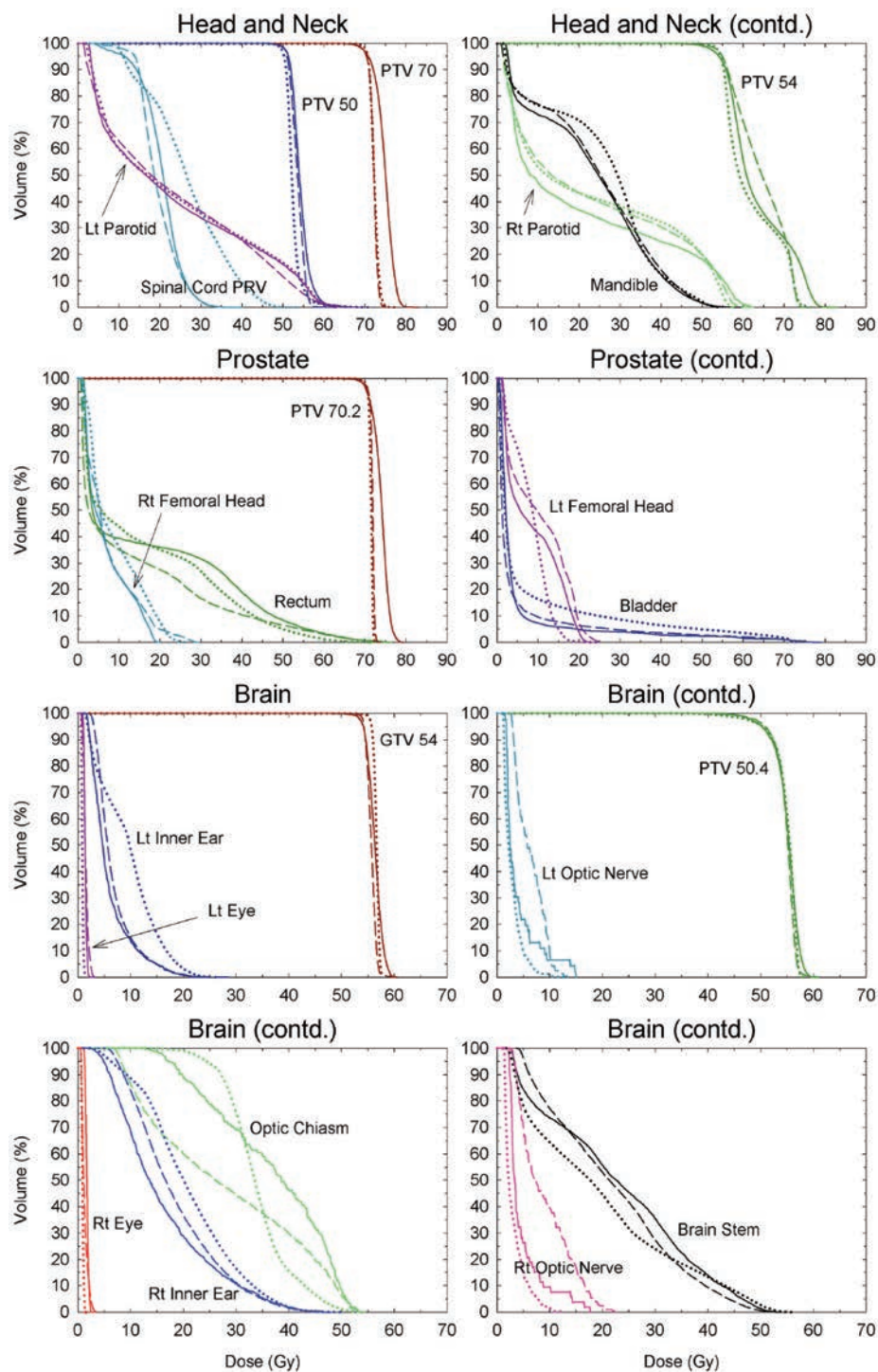
Similar calculations were performed using the evaluation tool in Eclipse with DVHs for the benchmark phantom generated from Eclipse. The TCP/NTCP values obtained with Eclipse were found to agree, within one percentage point, with those generated by Pinnacle (Biological Response panel). For example, TCP/NTCP values for one of the rectangular structures were 0.81/0.19 and 0.80/0.18 for Pinnacle and Eclipse, respectively.

The presence of two different tools to calculate TCP and NTCP in Pinnacle (Biological Response panel and NTCP/TCP Editor) offers the user greater flexibility. The TCP model implemented in the NTCP/TCP Editor is not widely used in the literature, and a database of model parameters is not provided, which is likely to steer users toward the Biological Response panel for all TCP calculations. On the other hand, the LKB model implemented in the Editor is much more widely used than the Poisson-based NTCP model from the Biological Response panel. For both models, the origin of parameters included in the library can be traced to the organ tolerance data of Emami et al. (1991). It is therefore reasonable to hypothesize that the NTCP models in the Biological Response panel and NTCP/TCP Editor should provide similar estimates for the same endpoint and dose distribution. To test that, structures and endpoints for NTCP calculations in NTCP/TCP Editor were matched to those previously selected in the Biological Response panel. The two tools produce somewhat different values of NTCP, with the Editor giving smaller estimates for all structure/endpoint combinations. In one case, an NTCP estimate provided by the Editor was smaller by a factor of 2 than the corresponding estimate from the Biological Response panel (25% vs. 50%). Users should be cautioned against using models and parameter estimates of unverified origin, if predicted TCP/NTCP values are to be used for making clinical decisions. A similar warning statement is provided in the vendor's user manual. Alternatively, users can input their own or other validated data using the tools provided in the TPS.

#### **IV.D.2. Comparison of Plans Generated by Monaco, Pinnacle, and Eclipse Systems**

Treatment plans for three representative test cases designed using CMS Monaco (V1.0), Philips Pinnacle (V8.0h), and Varian Eclipse (V10.0) are compared in Figure 6. The head & neck plan shown in Figure 6 is the same that was used for the sensitivity studies (sections IV.A.2 and IV.B.3). The gEUD values computed based on these DVHs for selected organs are tabulated in Table VIII. The gEUD values were calculated based on the power law [Eq. (1)] and the parameter  $a$  used is included in the table. All Monaco plans resulted in substantially less homogeneous target dose distributions compared to the Pinnacle and Eclipse plans. This result is a consequence of the compulsory cell killing objective which penalizes small cold spots less drastically than physical minimum dose penalties and the practice of normalizing the treatment plans to the minimum dose in the target, not to equivalent target EUD (note that Monaco also allows users to supplement the target EUD cost function with physical constraints). In terms of OAR sparing, the three TPS produced plans of similar quality for the head & neck case, with the exception of the spinal cord PRV dose in the Eclipse plan. In the prostate case, Pinnacle offers somewhat better sparing of the rectum at low and intermediate doses. It has been previously demonstrated that one can use Monaco to generate plans with substantially better OAR sparing compared to the plans designed using DV-based TPS XiO (Semenenko et al. 2008). The same trend has been observed for plans created in Pinnacle using biological vs. DV-based cost functions (Qi et al. 2009), similar to those reported previously (Wu et al. 2002, 2003, 2005).





**Figure 6.** DVHs for head & neck, prostate, and brain cases obtained using biologically based optimization features implemented in CMS Monaco (solid lines), Philips Pinnacle (dashed lines), and Varian Eclipse (dotted lines).



**Table VIII.** gEUD (Gy) Values Calculated Based on the DVHs for Three Sample Plans along with the Parameter  $a$  Used.

Case	Organs	$a$ Value	Monaco	Pinnacle	Eclipse
Head & Neck	PTV 70	-10	74.40	71.99	72.15
	PTV 54	-10	59.59	61.04	59.01
	PTV 50	-10	53.79	53.25	52.13
	Cord PRV	20	27.19	27.77	39.91
	Lt parotid gland	1	23.12	23.12	23.61
	Rt parotid gland	1	20.57	23.05	23.11
	Mandible	10	38.52	38.66	38.78
Prostate	PTV 70.2	-10	73.61	71.77	71.41
	Rectum	8	46.11	44.61	41.30
	Bladder	8	43.21	43.00	45.79
	Lt femoral head	12	14.76	20.09	18.21
	Rt femoral head	12	16.86	18.43	13.90
	Pubic bone	12	41.25	41.19	49.06
Brain	GTV 54	-10	56.08	55.55	56.56
	PTV 50.4	-10	54.11	53.90	53.26
	Brain stem	16	41.61	40.06	42.80
	Optic chiasm	16	46.11	44.99	41.68
	Lt eye	16	1.94	2.29	1.08
	Rt eye	16	2.04	2.45	1.13
	Lt optic nerve	16	12.33	10.12	8.68
	Rt optic nerve	16	14.07	17.16	8.61
	Lt inner ear	16	16.28	18.60	18.22
	Rt inner ear	16	34.36	34.00	34.57

Lt = Left  
Rt = Right

## **V. ACCEPTANCE, COMMISSIONING, AND ROUTINE QA TESTS FOR BIOLOGICALLY BASED PLANNING SYSTEMS**

The acceptance, commissioning, and periodic QA tests recommended by previous TG reports [TG-40, Kutcher et al. (1994); TG-53, Fraass et al. (1998); TG-119, Ezzell et al. (2009); TG-142, Klein et al. (2009)] for general TPS features (e.g., data input/output, dose calculations, plan deliverability, clinical software tools) should be performed for BBTPS. These recommendations will not be repeated here. The aim of this section is to provide examples of the additional QA tests specific to general features pertinent to BBTPS. Physicists are encouraged to develop their own QA tests specific to the BBTPS in use at their clinics. It is expected that a more complete list of such QA tests will become available as more practical experience is gained in the future. All acceptance and commissioning tests should be carried out on the system after it has been installed in the clinic but before it is used clinically.

### **V.A. ACCEPTANCE TESTS**

Based on the previous TG reports [TG-40, Kutcher et al. (1994); TG-53, Fraass et al. (1998)], an acceptance test is performed to confirm that the TPS performs according to its specifications. Because the quantifiable and testable specifications are generally lacking for a BBTPS at the present time, the acceptance testing may be limited to verify functionalities offered by the BBTPS. Examples of these functionalities that might be included in the acceptance testing are: (1) allowing user to update model and/or model parameters, (2) allowing user to specify model-based goals and constraints for optimization, and (3) allowing user to evaluate plan based on biological metrics.

### **V.B. COMMISSIONING TESTS**

#### **V.B.1. Selective Verification of Biological Metrics**

Biological metrics, i.e., EUD/TCP/NTCP, calculated within a TPS should be independently verified by the user for selected cases before routine clinical use and after major upgrades. The benchmark phantom used in this report (section IV.D.1) may be used in this verification. If fully validated by the medical physics community, other research software tools, such as CERR (Deasy et al. 2003) at <http://radium.wustl.edu/CERR/about.php>, BIOPLAN (Sanchez-Nieto and Nahum 2000), or BioSuite (Uzan and Nahum 2009), may be used as evaluation tools. TPS vendors are urged to provide detailed descriptions of all implemented models and parameter values to make this possible. It is also recommended that TPS vendors provide tools to export dose distributions, DVHs, and 3D dose matrices to external programs. Note that results may differ whether EUD/TCP/NTCP is calculated using the dose grid or DVH (section III.A.4). TPS documentation should clearly state the technique used to calculate all biological metrics.

#### **V.B.2. Double Planning**

It is recommended that for the first several cases from each representative tumor site, new users of BBTPS prepare second plans using their standard DV-based TPS. New and traditional plans

can be compared to help understand how different aspects of a dose distribution are controlled by biological cost functions. Preparation of backup plans may be discontinued after sufficient expertise in treatment planning and knowledge of advantages/limitations the BBTPS have been gained.

### **V.B.3. Compilation of Benchmark 3D Datasets and DVHs for Major Sites**

The task group has prepared sample plans for the benchmark phantom and three test cases representing major sites often treated using IMRT: head & neck, prostate, and brain. Image and structure sets in the DICOM format as well as tabular DVH data for these three cases can be downloaded from:

- <http://www.aapm.org/org/committees/TG166/TG166prostate.zip>,
- <http://www.aapm.org/org/committees/TG166/TG166headneck.zip>,
- <http://www.aapm.org/org/committees/TG166/TG166brain.zip>, and
- [http://www.aapm.org/org/committees/TG166/EUD\\_Monaco\\_Pinnacle\\_Eclipse.xls](http://www.aapm.org/org/committees/TG166/EUD_Monaco_Pinnacle_Eclipse.xls).

Note that these sample plans do not necessarily represent the best plans possible for the cases. They are provided for comparison purposes. Physicists attempting to commission a BBTPS may compare plans obtained with their system to these sample plans and may explore whether similar or better plans can be obtained with the BBTPS in question. If applicable, the EUD values provided for these sample plans in Table VIII may be used to validate the EUD calculation in the testing of BBTPS.

### **V.C. PROCEDURES FOR ROUTINE QA**

It is suggested that users of biologically based TPS prepare an IMRT sample plan generated by the biologically based plan optimization based on either one of the benchmark cases or the user's own case at the time of commissioning. This sample case should be re-planned annually or after major upgrades and compared to the baseline data, i.e., DVHs, EUD/TCP/NTCP, to ensure that models, parameters, and algorithms implemented in the TPS plan optimization remain the same. For a BBTPS with a biologically based plan evaluation tool, users should prepare a 3D dose distribution based on one of the benchmark cases or the user's own case and obtain its baseline DV and biological metrics using the evaluation tool at the time of commissioning. These metrics should be re-evaluated annually or after major upgrades. The new metrics should be identical to the baseline data. For TPS capable of Monte Carlo dose calculations, a non-stochastic dose calculation algorithm should be used, if available, for initial and subsequent treatment planning to eliminate statistical uncertainties associated with the Monte Carlo method (section III.A.4).

## VI. VISION OF TG-166 FOR FUTURE DEVELOPMENT OF BIOLOGICALLY BASED TREATMENT PLANNING

### VI.A. EVOLUTION OF BIOLOGICALLY BASED TREATMENT PLANNING SYSTEMS

A TG-166 vision for current and future developments in BBTP is summarized in Table IX. The majority of existing TPS employ DV-based cost functions for treatment plan optimization. Plan evaluation is also performed using DV criteria, i.e., 3D dose distributions and DVHs. Although some of the existing systems provide tools for calculation of TCP/NTCP with a purpose of plan evaluation, these tools are not well documented and are not supplied with databases of reliable model parameters and therefore have not found a widespread use among radiation treatment planners or evaluators. This state of affairs is designated as Stage 0 in the proposed BBTP evolution scheme.

Initial transition to Stage 1 has occurred with an emergence of the first TPS employing EUD-based cost functions for plan optimization (section IV). TPS representative of this stage may provide framework not only for biologically based optimization (e.g., CMS Monaco), but may also offer practical tools for biologically based plan evaluation (e.g., Philips Pinnacle). Incorporation of plan comparison tools based on EUD, TCP, NTCP, and uncomplicated tumor control probability (UTCP) functions into commercial TPS is a welcome development. Provided that such tools are intuitive and easy to use, a greater number of radiation oncology professionals will be willing to gradually integrate biological metrics into their clinical practice, which will facilitate transition to Stage 2 in the evolution of BBTP.

**Table IX.** Evolution of BBTP.

Evolution Stage	Plan Optimization Strategy	Plan Evaluation Strategy	Representative TPS
0	DV-based cost functions	DVHs	All IMRT TPSs
1	EUD for OARs; EUD- and DV-based cost functions for targets	DVHs and relative values of TCP/NTCP/UTCP	CMS Monaco Philips Pinnacle Varian Eclipse
2	EUD-based cost functions for all structures	Absolute values of TCP/NTCP/UTCP	Future developments
3	Absolute values of TCP/NTCP/UTCP	Absolute values of TCP/NTCP/UTCP	Future developments

The principal difference between Stages 1 and 2 is that TCP and NTCP functions will play a more important role in the treatment plan evaluation process and will supersede DV metrics as the major indicators of plan quality. As opposed to the use of TCP and NTCP in Stage 1, where these estimates are used primarily in a relative fashion as an ancillary tool to compare alternative treatment plans, in Stage 2 the growing confidence in predictive power of dose-response models will allow decisions about plan quality to be based on absolute estimates of TCP/NTCP. Because the effectiveness of a plan will be judged by the predicted biological outcome, dose-based constraints will no longer be required to force target dose to be as uniform as possible so long as the plan results in desired values of TCP and inhomogeneous target doses do not jeopardize intermixed normal tissues; and therefore treatments could be optimized based on EUD-based cost functions alone. Stage 2 must be accompanied by clear supporting evidence for the reliability of each model used and may be adopted at different times for different disease sites.

Transition to non-uniform target dose distributions represents a major paradigm shift in treatment planning. The requirement for uniform dose delivery was a long-standing tradition in our field. It may have been based on the assumption that tumors behave as “parallel structures,” and that the ultimate TCP will be related to the minimum dose. Seeking a uniform target dose that exceeds the desired minimum was a way to reduce the overall integral dose/exposure to the patient. This concept has also been rooted in convention (ICRU 1993, Report 50). However, there is no proof that this construct is valid for tumors. Relaxing target uniformity constraint, and allowing hot spots within the target, may afford the planner increased flexibility in creating a better plan that may lead to better critical structure sparing (De Gersem et al. 1999). Table X summarizes arguments in favor and against using heterogeneous dose distributions. While most of the supporting arguments are theoretical, there are some examples where non-uniform dose delivery has proven to be safe and effective, e.g., brachytherapy, intracranial SRS, and simultaneously integrated boost. It is also known that, due to organ motion and daily setup uncertainties, actual delivered dose distributions are less homogeneous than the planned dose distributions, especially if small margins are used (Killoran et al. 1997). This implies that several generations of radiation oncologists have been treating patients using moderately inhomogeneous dose distributions.

The ultimate BBTP (Table IX, Stage 3) is represented by a scenario in which treatment plans will be optimized using objective scores based on TCP/NTCP (e.g., Källman et al. 1992a; Brenner and Sachs 1999). The optimized values of TCP and NTCP will be used directly to evaluate treatment plans.

**Table X.** Pros and Cons of Homogeneous versus Heterogeneous Tumor Dose Distributions.

	Homogeneous Dose	Partial Tumor Boosts	Heterogeneous Dose
<b>Pros</b>	<p>Proven track record.</p> <p>Consistent with classical radiobiology.</p> <p>Less ambiguity in reporting and analyzing delivered doses.</p> <p>Hot spots are probably useless unless they cover most of the tumor or the most resistant sub-volume.</p> <p>Most logical approach if information about tumor heterogeneity is not available.</p>	<p>Predicted to be effective under a wide range of theoretical assumptions.</p> <p>Easy to do using IMRT.</p> <p>The PTV margin provides a natural “draw-down” region between a GTV boost and critical normal structures.</p>	<p>Adds another degree of freedom to the treatment planning problem and can lead to better critical structure sparing.</p> <p>Hot spots may not be detrimental if they are located inside the GTV.</p> <p>Because tumors are heterogeneous (e.g., positron emission tomography (PET) imaging), there is no reason that tumor dose should be uniform.</p> <p>Would allow biological targeting via the use of PET, etc.</p> <p>Stereotactic and implant experience is supportive although in different dose/dose-rate regimens.</p>
<b>Cons</b>	<p>Old school/tradition-driven.</p> <p>Opportunity to exploit tumor heterogeneities is lost.</p> <p>Opportunity to use the flexibility of IMRT is limited.</p> <p>Mounting data support the notion that heterogeneous dose may be advantageous.</p>	<p>No consistent human or animal data to confirm positive effects, although supportive data can be found for certain tumor sites.</p> <p>Due to temporal changes in tumor volumes, effect of partial tumor boost may be diminished.</p>	<p>No consistent human or animal data to confirm positive effects, although supportive data can be found for certain tumor sites.</p> <p>Theoretical benefits are limited by the accuracy of TCP models.</p> <p>Effect of cold spots may be underestimated, especially if cold spots are located in the GTV.</p> <p>Must be careful that hot spots within the PTV are located within the GTV, and not the normal tissue margin.</p>



## VI.B. DESIRED FEATURES AND FUNCTIONALITIES FOR FUTURE BIOLOGICALLY BASED TREATMENT PLANNING SYSTEMS

It is instructive to speculate as to what constitutes an ideal (optimal) BBTPS. Many preferred general features for TPS (e.g., fast and accurate dose calculation and optimization algorithms, same dose engine for optimization and for forward calculation, accurate DVH generation, robust and effective input and output tools) are also important for future BBTPS. In addition, the following characteristics and functionalities are desirable for a BBTPS:

- (1) The system should allow the user to input or to update models and model parameters for both plan evaluation and optimization. A library of model parameters, containing the default parameter values with capability of allowing user to update these parameters based on specific clinical situation or local patient population, should be provided. The system should supply detailed documentation for the models and the default parameter sets (their origin, applicability, and provenance). For example, the LKB NTCP model along with a database of parameters for common organs and endpoints, indicating the sources (e.g., QUANTEC), should be provided. For an updated model, inclusion of new biological or medical factors might introduce additional uncertainties. The user should be provided with the tools to do the calculations based on both latest and previous models. As there may be competing models for a given clinical situation, the user should have a choice regarding which model should be used for the situation. There might be clinical reasons to trust one type of model over others in certain situations. The system should allow user to consider organ interaction (e.g., interaction between heart and lung, or liver and kidney) by modifying model(s) and/or selecting model parameters. Note that some of these features are included in the existing TPSs (e.g., Pinnacle).
- (2) The system should allow combinations of biological model- and DV-based constraints for all structures in the optimization. For example, one might want to use lung EUD (or LKB NTCP model) but also keep  $V_{20}$  below 35%. The maximum dose may be used as hard constraint to limit hot spot. For some organs, the user may choose to use DV constraints only. (For example, the uniform dose that approaches the tolerance dose for brainstem may be used in the overlap region of brainstem and glioma PTV.) For certain situations, a hybrid approach, e.g., using DV-based optimization followed by biologically based optimization (Das 2010), may be helpful.
- (3) The optimizer should “reward” getting lower NTCP than requested, if that is possible without violating the higher priority goals or preventing lower priorities from being achieved, and should allow maximizing TCP for a given NTCP or minimizing NTCP for a given TCP.
- (4) The system should allow the user to define “stop values” for iteration during plan optimization. For example, the plan optimization may attempt to lower EUD or NTCP for normal tissue no matter what they are. The user-defined value below which further optimization is unnecessary would improve efficiency of the optimization.

- (5) The user should be able to input “dose-modifying factors” to account for the effects of certain medical factors such as the use of chemotherapy, pre-existing conditions (e.g., diabetes), and lifestyle choices (e.g., tobacco use), or biological factors such as genetic predispositions to a complication. For example, if chemotherapy is known to be a factor, the user can choose either using a different set of model parameters, or introducing a dose-modifying factor. The system should provide the user with the opportunity to assess the potential variations in outcome with changes in these factors. For example, estimations such as “this plan is anticipated to increase the patient’s risk of lung cancer by xx%, and this risk can be reduced to yy% if the patient discontinues smoking tobacco” could be informative.
- (6) The system should have connectivity with medical information systems such that clinical parameters that might be used in optimization (e.g., pulmonary function tests) can be accurately and directly incorporated. Similarly, clinical information within the medical information systems may be needed to determine which predictive model(s) to use. For example, the predictive models for pneumonitis might be different for patients with cancers of the lung vs. breast.
- (7) The system should provide an option to assess the outcomes of a tentative plan reflective of anticipated delivery uncertainties including setup errors, inter- and intrafractional anatomic variations. The system should allow building a population-based or patient-specific probability distribution into the evaluation of TCP and NTCP, perhaps with “confidence limited” NTCPs and TCPs for a given population-based or patient-specific motion probability distribution.
- (8) For a given treatment, the best achievable dose distribution depends on the patient geometry and the physical limitations of the radiation in question. For example, the minimal dose to an OAR adjacent to the PTV mostly depends on the distance between the OAR and PTV and the physical characteristics of the radiation beam and the degradation in target coverage (TCP) that the physician is willing to accept. It is desirable that the TPS can estimate best possible NTCP conditional on a chosen TCP, avoiding the unnecessary effort in search for non-achievable plans.
- (9) Models should allow for spatial radiobiological variations (e.g., clonogenic cell density, radiosensitivity, hypoxia) linking to biological/functional images. The planning system should provide a “painting-by-number” feature (Ling et al. 2000; Wu et al. 2005). That is, the user should be able to generate a highly non-uniform dose distribution based on the spatially varying biological/functional information. Plan evaluation tools, such as the functional DVH (fDVH) (Lu et al. 1997; Marks et al. 1999) that can take into account the spatial distribution of the functional importance, should be provided.
- (10) Outcome models should be able to consider time effects (e.g., treatment breaks, fractionation, tumor growth, and delivery time). The system should have the capability to optimize around a prior dose distribution either from external beams or from brachytherapy. Validated deformable registration for calculating delivered dose from previous treatment courses should be available.
- (11) The system should have user-friendly graphic tools to show information during the optimization process. This information includes table with constraints and priorities,

graphs displaying components of cost function (biologically based and/or DV-based constraints), DV and/or biological indices as in the current iteration.

- (12) For plan evaluation, the calculation of biological indices should be accompanied by parameter sensitivity analysis. Ability to renormalize/adjust a plan to achieve biological goals is also useful. For example, in addition to being able to renormalize the plan according to DV criteria (e.g., 98% of PTV receives at least 95% prescription dose) renormalize to achieve an acceptable value of NTCP or EUD for a given OAR.

## VII. SUMMARY OF RECOMMENDATIONS AND PRECAUTIONS FOR CLINICAL USE OF BIOLOGICALLY BASED MODELS

### VII.A. GENERAL RECOMMENDATIONS

Biologically based cost functions for OARs may be preferable to DV constraints because the former typically controls entire portions of the DV domain whereas the latter controls only a single point. For OARs requiring more than one DV constraint for inverse treatment planning, it may be preferable to replace multiple constraints by a single EUD-based cost function with appropriate choice of a volume effect parameter. Because a biological cost function controls greater space in the DV domain, it may be more effective in optimizing a plan towards OAR sparing as compared to the use of DV constraints.

Currently implemented biological cost functions for target volumes control only cold spots. These functions are not essential to obtain good quality plans and may be replaced with minimum dose constraints on target dose even in biologically based optimization.

Biological cost functions for target volumes do not effectively control hot spots. Despite some evidence in favor of less homogeneous target dose distributions, TG-166 maintains that highly non-uniform dose distributions caused by the optimization technique (as opposed to deliberate and tested non-uniformity as is seen in SRS, simultaneously integrated boost techniques, and brachytherapy) should be avoided. To obtain clinically acceptable plans with respect to target dose homogeneity, biological cost functions should be supplemented with maximum-dose-type physical cost functions.

At present, the plan evaluation should be performed based on established DV criteria. Therefore, biologically based TPSs must present physical parameters (i.e., DVHs; minimum, maximum, mean dose) along with any biological metrics. EUD can be used to rank plans provided the parameter  $a$  is calibrated appropriately. Relative estimates of biological indices (i.e., TCP, NTCP, and UTCP) may be used to help select rival plans, provided that the users understand the range of applicability of models and parameter values implemented in their TPS. Use of absolute estimates of TCP/NTCP as main indicators of plan quality is not warranted at this time.

Regardless of advancement of biological tools for treatment planning, TG-166 recommends that review of 3D dose distributions always remain a part of the treatment plan evaluation process. TPSs should allow the dose to be viewed in multiple planes (e.g., axial, coronal, and sagittal, as well as non-standard planes and an overall volumetric display) since hot spots in non-specific tissues and heterogeneities in physiology/function within tumor/normal tissues are sometimes more clearly understood in these other planes.

If the parameter  $a$  cannot be calibrated in the calculation of EUD, the following generic values may be used as starting values:  $a = 1$  for a parallel organ and  $a = 8$  for a serial organ. An uncertainty analysis should be performed by calculating a type of confidence interval around the calculated EUD values, for example, by calculating the lower and upper bounds on the EUD using  $a = 0.5$  and  $a = 3$  for parallel structures, and  $a = 4$  and  $a = 15$  for a serial structures.

## VII.B. TPS-SPECIFIC RECOMMENDATIONS

The recommendations below apply to the specific system versions described in section IV.

### VII.B.1. CMS Monaco

Commonly found values for the cell sensitivity of tumors of  $\sim 0.25 \text{ Gy}^{-1}$  frequently do not penalize cold spots as forcefully as demanded by clinical practice, so that higher values of cell sensitivity may have a greater utility, if less biological meaning. However, for the selected test case (section IV.A.2), the choice of cell sensitivity parameter had minimal impact on the minimum PTV dose.

The Poisson statistics cell kill model should always be used in conjunction with a physical constraint, either the Maximum dose or Quadratic overdose penalty. Failure to specify the second cost function results in convergence problems and long running times.

Reasonable starting points for EUD constraints can be derived by an EUD computation for a number of acceptable dose distributions in each institution. Typically, without biological optimization the EUD values will be spread out over an interval of values. A good starting point could be the median of this distribution, meaning that half of the patients could get a lower EUD by means of biologically constrained optimization.

### VII.B.2. Philips Pinnacle

By adjusting the volume parameter, the Max EUD objective can be used to specify optimization goals for all types of OARs.

In case of a single PTV, combining the Target EUD objective with the Uniformity constraint yields good results.

For plans with multiple PTVs, using Min dose and Max dose cost functions offers better control over target dose distributions.

### VII.B.3. Varian Eclipse

Use of Min/Max dose or percentage structure volume at dose provides more reliable control over target dose distributions. Effect of adding EUD or TCP models should be carefully monitored to avoid introducing target dose heterogeneities that would not be accepted in clinical plans.

Adjusting  $TD_{50}$  and  $n$  values in LKB model can be used to shape evolution of OAR DVH in optimizer.

Adjusting volume parameter and target EUD can be used to shape the DVH on OARs.

## APPENDIX A

### cEUD: Cell Killing-Based Equivalent Uniform Dose

TG-166 proposes a new term—“cell killing-based EUD” or “cEUD”—to help distinguish a class of expressions based on mechanistic models of cell killing (Niemierko 1997) from the empirical generalized equivalent uniform dose (gEUD) formula (section II.A). cEUD is derived by equating survival fractions or TCP for the equivalent uniform and the true non-uniform dose delivery scenarios. In its most simplified form, cEUD is given by (Niemierko 1997):

$$\text{cEUD} = D_{\text{ref}} \frac{\ln \left[ \sum_i v_i (\text{SF}_2)^{D/D_{\text{ref}}} \right]}{\ln(\text{SF}_2)}, \quad (\text{A1})$$

where  $D_{\text{ref}} = 2$  Gy is the reference dose,  $\text{SF}_2$  is the surviving fraction at the reference dose, and  $(D_i, v_i)$  are bins of a differential DVH for the non-uniform distribution of interest. The underlying assumption in the Eq. (A1) is that cell survival can be approximated by an exponential function of dose. This is a valid assumption for tumor cell survival typically characterized by large  $\alpha/\beta$ , of the order of 10 Gy. The other assumption is that dose distribution is nearly homogenous, which also typically holds for tumors. cEUD is independent of the total number of clonogens.

Other radiobiological details, such as non-uniform spatial distribution of clonogens, dose-fractionation effects, interpatient heterogeneity, etc., can be easily incorporated into the expression for cEUD at the expense of additional parameters (Niemierko 1997).

cEUD is relatively insensitive to the level of inter-patient heterogeneity and the value of  $\alpha/\beta$  ratio used for dose-per-fraction corrections, and therefore the simplest version of cEUD [Eq. (A1)] can often be used with sufficient accuracy (Niemierko 1997). Comparisons of cEUD with the TCP model incorporating interpatient heterogeneity [Eq. (B3)] show that cEUD is a more robust concept, which implies that it is safer to use in the environment of large uncertainties in radiobiological parameters (Ebert 2000). These properties make cEUD an attractive quantity for BBTP.

## APPENDIX B

### Extension of Poisson-Based TCP Model to Account for Repopulation and Interpatient Heterogeneity

To account for repopulation, the LQ survival probability is often multiplied by an exponential term (Fowler 1989)  $\exp[\eta \max(T - T_k, 0)]$ , where  $\eta$  is the proliferation rate (note that this parameter is usually designated by  $\gamma$  in the literature, but it is assigned a different symbol in this report to avoid confusion with the slope parameter),  $T_k$  is the time at which repopulation begins after the start of treatment, and  $T$  is the overall treatment time. The expression for TCP then becomes

$$\text{TCP} = \exp \left[ -N \exp \left\{ -D \left( \alpha + \beta \frac{D}{n} \right) + \eta \max(T - T_k, 0) \right\} \right]. \quad (\text{B1})$$

This model can be easily extended to a case of non-uniform dose distribution in the tumor:

$$\text{TCP} = \prod_i \text{TCP}(D_i, v_i) = \exp \left[ -\rho \sum_i v_i \exp \left\{ -D_i \left( \alpha + \beta \frac{D_i}{n} \right) + \eta \max(T - T_k, 0) \right\} \right], \quad (\text{B2})$$

where  $\rho$  is the clonogen density, here assumed to be uniform throughout the tumor, and  $v_i$  is the fractional volume of the tumor irradiated to a dose  $D_i$ . For practical calculations, bins of a differential DVH,  $(D_i, v_i)$ , may be used.

Equation (B1) has been used (sometimes with omission of the time factor) in a number of studies to estimate parameters from clinical data (e.g., Brenner 1993; Roberts and Hendry 1993; Wu et al. 1997) and found to yield unreasonably low estimates of  $\alpha$  and  $N$  (King and Mayo 2000). Some authors (Zaider and Minerbo 2000; Brenner et al. 2002) argue that this is a correct result because tumor control requires the eradication of a very small number of highly radioreistant clonogens, but more often, these findings may be attributed to a failure of Eq. (B1) to account for inter-patient heterogeneity in the model parameters, particularly  $\alpha$ , which would inevitably be present in any clinical cohort (Suit et al. 1992; Brenner 1993; Webb 1994; Webb and Nahum 1998). Webb and Nahum (1993), Webb (1994), and Nahum and Sanchez-Nieto (2001) have modeled interpatient heterogeneity by assuming that  $\alpha$  is normally distributed with the mean  $\bar{\alpha}$  and standard deviation  $\sigma_\alpha$ :

$$\text{TCP} = \exp \left[ -N \exp \left\{ -D \left( \alpha + \beta \frac{D}{n} \right) + \eta \max(T - T_k, 0) \right\} \right]. \quad (\text{B3})$$

where  $\text{TCP}(\alpha)$  is given by Eqs. (B1) or (B2). Roberts and Hendry (1998) have proposed a closed-form TCP model incorporating interpatient heterogeneity that has the same number of adjustable parameters (five) as Eqs. (B1) or (B2).



## APPENDIX C

### Critical Element and Critical Volume Models

The critical element or serial model is premised on a simple argument that, if the probability of failure for a single FSU,  $p$ , is known, the probability of failure for an entire organ composed of  $N$  FSUs arranged in a series can be calculated as  $1 - (1 - p)^N$  [e.g., Withers et al. (1988)]. Additional mathematical manipulations [see Schultheiss et al. (1983) and Niemierko and Goitein (1991) for details] allow expressing NTCP for a non-uniformly irradiated organ through a complication probability for the entire organ irradiated uniformly,  $P(D_i)$ :

$$\text{NTCP} = 1 - \prod_i [1 - P(D_i)]^{v_i}, \quad (\text{C1})$$

where  $v_i$  is the fractional organ volume receiving a dose  $D_i$ . The dose-response relationship for a uniformly irradiated organ is often described empirically by the log-logistic function (Eq. 11). The model directly accommodates non-uniform dose distributions and does not require a separate DVH reduction algorithm.

The critical volume or parallel model (Withers et al. 1988; Niemierko and Goitein 1993; Yorke et al. 1993; Jackson et al. 1993) hypothesizes that NTCP for a parallel-type organ is related to the fraction of FSUs that are destroyed by radiation rather than the absolute number of damaged FSUs. The complication occurs when this fraction, denoted the fraction damaged or  $f_{dam}$ , exceeds some critical value referred to as “functional reserve.” For a non-uniformly irradiated organ or tissue, the fraction damaged is calculated according to

$$f_{dam} = \sum_i v_i P(D_i), \quad (\text{C2})$$

where  $v_i$  is the fractional organ volume receiving a dose  $D_i$  and  $P(D_i)$  is the probability of destroying a single FSU following a uniform irradiation with the dose  $D_i$  (Jackson et al. 1995). The probability  $p(D_i)$  is often expressed using the empirical sigmoid relationship given by Eq. (11), where the two parameters have the same meaning as described above but refer to the response of an individual FSU rather than the entire organ (Jackson et al. 1995; Yorke et al. 2002).

In order to relate  $f_{dam}$  to clinically observed complication rates, a distribution of functional reserves among the patient population must be specified. Jackson et al. (1995) used the normal distribution involving two additional parameters to describe the population mean and the standard deviation of functional reserves, which brings the total number of parameters to four. To avoid specifying these extra parameters for the parallel model, it is often considered practical to directly use  $f_{dam}$  for treatment evaluation and optimization (Yorke et al. 2002).

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