doi:10.1016/j.ijrobp.2009.07.1754

INTRODUCTORY PAPER

USE OF NORMAL TISSUE COMPLICATION PROBABILITY MODELS IN THE CLINIC

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The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) review summarizes the currently available three-dimensional dose/volume/outcome data to update and refine the normal tissue dose/volume tolerance guidelines provided by the classic Emami *et al.* paper published in 1991. A "clinician's view" on using the QUANTEC information in a responsible manner is presented along with a description of the most commonly used normal tissue complication probability (NTCP) models. A summary of organ-specific dose/volume/outcome data, based on the QUANTEC reviews, is included.   © 2010 Elsevier Inc.

QUANTEC, NTCP.

INTRODUCTION

Historically, radiation therapy (RT) fields/doses were selected empirically, based largely on experience. Physicians relied on clinical intuition to select field sizes/doses. They understood that these empiric guidelines were imprecise and did not fully reflect the underlying anatomy, physiology, and dosimetry.

A great promise of three-dimensional (3D) treatment planning was quantitative correlates of doses/volumes with clinical outcomes. This promise was partly delivered. When 3D dosimetric information became widely available, guidelines were needed to help physicians predict the relative safety of proposed treatment plans, although only limited data were available. In 1991, investigators pooled their clinical experience, judgment, and information regarding partial organ tolerance doses, and produced the "Emami paper" (1). While "Emami" is often criticized, the paper clearly stated the uncertainties and limitations in its recommendations, and it is widely admired for addressing a clinical need.

During the last 18 years, numerous studies reported associations between dosimetric parameters and normal tissue outcomes. The QUANTEC (**qu**antitative **a**nalysis of **n**ormal **t**issue **e**ffects in the **c**linic) articles summarize the available data to update/refine the estimates provided by Emami *et al.* A central goal of QUANTEC is to summarize this information in a clinically useful manner.

We hope the information will improve patient care by providing clinicians and treatment planners with tools to estimate "optimal/acceptable" 3D dose distributions. We hope that at least some of the summary tables, graphs, and models presented will be reproduced and posted in resident workrooms, dosimetry planning areas, and physician offices, as is currently done with the Emami *et al.* tables.

The information provided by QUANTEC is not ideal, and care must be taken to apply it correctly in the clinic. We herein present a "clinician's view" on using the QUANTEC information in a responsible manner, highlighting the diverse type of limitations of the presented data.

LIMITATIONS INHERENT IN EXTRACTING DATA FROM THE LITERATURE

The information presented is largely extracted from publications. Because different investigators often present information differently (*e.g.,* actuarial vs. crude complication rates), pooling data from multiple studies may be inaccurate.

Summary tables are often included to help the reader better understand the primary data.

LIMITATIONS OF PREDICTIVE MODELS

Some studies use models to estimate the complication risk. Care should be taken when applying models, especially when clinical dose/volume parameters are beyond the range of data used to generate the model/parameters. Models and dose/volume recommendations are only as good as the data available. Typically, they are based on dose–volume histograms (DVHs). DVHs are not ideal representations of the 3D doses as they discard all organ-specific spatial information (and hence assume all regions are of equal functional importance), and often do not consider fraction size variations. They are usually based on a single planning computed tomography (CT) scan that does not account for anatomic variations during therapy (Fig. 1). Interinstitutional/physician differences in image segmentation, dose calculation, patient populations, and preferred beam arrangements may limit model exportability. Before introducing a predictive model into a clinical practice, it is prudent to assess if its predictions "make sense" in regard to that clinic's treatment plans and experience.

EVOLVING FRACTIONATION SCHEDULES

RT-induced normal tissue responses are fraction size dependent. Throughout the QUANTEC reviews, this variable is acknowledged and, where possible, considered by making adjustments for fraction size based on the linear quadratic (LQ) model. Nevertheless, α/β ratios are uncertain. Particular care must be taken when QUANTEC information is applied to stereotactic RT, where the fraction size is much different than that in the cited literature. For very novel fractionations, even the validity of the LQ model is questioned (2).

Even when the prescribed tumor dose is "conventionally" fractionated, the fraction size seen by the normal tissue may have varied over time. When "Emami" was published, most external RT was delivered with opposing fields, and shrinking field techniques—the normal tissue was irradiated with a fairly uniform fraction size. Modern techniques often use multiple beams (with or without concurrent boosts); the volume of normal tissue exposed to low doses is often increased and the dose is delivered at fraction sizes ranging from ≈ 0 to the prescribed fraction size.

COMBINED MODALITY THERAPY

Use of sequential/concurrent chemotherapy/RT is increasing for many tumors. Concurrent chemotherapy is typically believed to exacerbate the severity of normal tissue reactions, but data quantifying this is often lacking. Even when such data are available, the chemotherapy doses, schedules and agents—which may influence outcomes—are in evolution.

HOST FACTORS

Host factors (*e.g.,* chronic liver disease, genetic, lifestyle) may affect dose–response relationships and are partly respon-
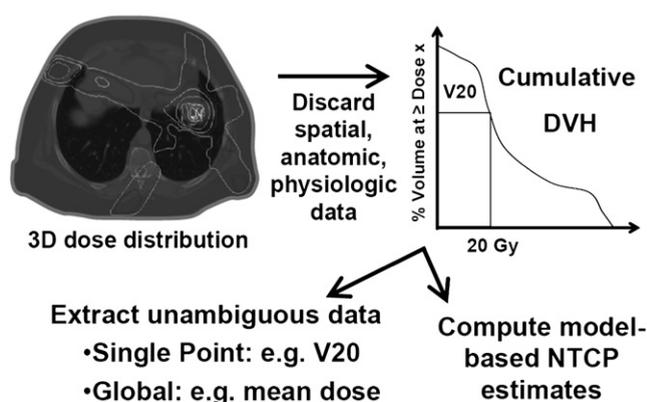

Fig. 1. A three-dimensional dose distribution is reduced to a two-dimensional (2D) dose–volume histogram (DVH) by discarding all spatial, anatomic and physiologic data. The 2D graph is then further reduced to a single value of merit, such as the mean dose, the percent of the organ receiving ≥ 20 Gy (V20), or a model-based normal tissue complication probability (NTCP).

sible for the shallowness of these relationships in the patient population. It is likely that incorporating these factors, when they are known, will produce better models/correlations/predictors of toxicity.

BALANCING THE RISKS TO DIFFERENT ORGANS

Different morbidities vary in their clinical significance. Grade 2 toxicity has a different clinical meaning for the esophagus than for the rectum. Furthermore, different patients may have different levels of acceptance for injuries. When comparing competing treatment plans, there is usually a tradeoff; for example, should we accept a certain dose to the lung or to the esophagus? For most cases, modern treatments will redistribute, not eliminate, the dose to normal tissue. The fundamental problem of treatment planning is how to balance exposure of one organ against that of another. Unfortunately, there is no objective way to do this.

Investigators have considered the risks to multiple organs, and computed the probability of uncomplicated tumor control (3–5). Others have attempted to incorporate the relative *importance* of different toxicities by considering their impact on patients' quality of life. This approach generates a global figure of merit such as the "quality of life adjusted tumor control probability" (6, 7). The utility of this approach, although conceptually attractive, is not clear.

FOLLOW-UP DURATION

If dose–effect relationships for a late complication are derived from a patient population with very poor prognosis, they may be limited by lack of long-term follow-up, and not applicable to patients with a better prognosis (*e.g.,* applying brain toxicity from patients with high-grade glioma to patients with low-grade tumors).

The risk of normal tissue complication occurs in the context of a patient's expected longevity. Radiation therapy is an effective anti-cancer therapy and can provide good

palliation for patients with recurrent/metastatic/incurable disease. In these settings, concern for late normal tissue reactions often should not limit the application of RT. For example, reirradiation of the whole brain for recurrent brain metastases to cumulative doses well above tolerance can provide palliation for these challenging cases (8–10) for which concern about late toxicity may be unnecessary. Similarly, RT for locally advanced lung cancers may routinely exceed the normal dose limits for lung and heart. In these instances, there typically are no good alternative therapies available. Withholding thoracic RT because of the risk of pericarditis or pneumonitis may not be therapeutically rational.

These concerns are most applicable to recently trained radiation oncologists who are accustomed to using 3D dosimetric information for most of their clinical decision making. They may be uncomfortable in clinical settings where large RT fields need to be applied without 3D dosimetry in order to provide palliative effect. It is the physician's responsibility to tell dosimetrists/physicists when it is appropriate to proceed with treatment without a formal 3D dose/volume assessment and/or suspend the conventional departmental dose/volume guidelines.

RELATING "WHOLE TREATMENT" DVHS WITH ACUTE TOXICITIES

For some organs, a relevant acute toxicity may occur *during* the course of RT (*i.e.,* before the delivery of the entire RT course). Relating the incidence of such acute events to a DVH that reflects the whole treatment course may be somewhat illogical. It might be preferable to try to relate acute events to the dose delivered before symptom onset (or even to doses received a number of days before symptom onset, if there is a known latency time).

If a consistent set of treatment fields is used throughout the entire course of treatment (*e.g.,* no field reductions), the "whole course" DVH might be a reasonable surrogate for the 3D doses delivered before acute symptom onset. Therefore, in these situations, it still might be a reasonable to relate the risk of acute events to a DVH that reflects the whole treatment course.

However, field arrangements often change during therapy, thus altering the dose/volume parameters for the target organ (*e.g.,* initial AP-PA fields plus a subsequent off-cord boost). In these situations, the "whole-course" DVH is less likely to be a reasonable surrogate for the 3D doses delivered prior to the acute toxicity. Thus, some dose/volume/outcomes analyses for acute endpoints that consider the so-called whole-course DVH may be suspect.

Further complicating the issue is the fact that the duration of symptoms (that may also influence the scoring of toxicity), may be affected by RT dose delivered *after* the onset of symptoms. In this regard, the whole-course DVH may indeed be reasonable to consider in dose/volume/outcomes analyses.

A similar concern may apply for analyses of late effects. If a late toxicity results from a severe acute toxicity occurring *during* the course of RT, relating that late event to the whole-course DVH may also be suboptimal.

TUMOR COVERAGE VS. NORMAL TISSUE RISK

For most curative patients, a marginal miss is more serious than a normal tissue complication. For many tumors, recurrences are difficult to manage, cause severe morbidity, and usually result in mortality. Target coverage should generally not be compromised to reduce the normal tissue risks. This is exemplified by the experience from Israel in treating orbital lymphomas. In 24 tumors treated in 23 patients, intraorbital recurrence was seen in four of 12 (33%) of the tumors treated with conformal fields (including the radiographically defined gross tumor with margin), vs. none of the 12 tumors treated with conventional whole-orbit techniques (11). Similarly, investigators at Washington University noted a higher relapse rate in lung cancers closer to the spinal cord; perhaps reflecting compromised GTV coverage because of spinal cord protection (Ref. 12 and personal communication from J. Deasy, 2008). Engels *et al*. noted a *reduction* in 5-year biochemical disease-free survival rate (from 91% to 58%) in patients irradiated for prostate cancer with the addition of implanted seeds for localization, and tighter "PTV margins," with the intent of reducing exposure to surrounding normal tissues (13). The use of improved diagnostic imaging, and improved immobilization and image guidance during RT, may facilitate a more realistic PTV margin to be applied safely.

APPLICABILITY TO CHILDREN

In the young, a mosaic of tissues develop at different rates and temporal sequences. In adults, the same tissues are in a steady state with relatively slow cell renewal kinetics. The vulnerability of tissues to RT typically increases during the periods of rapid proliferation. Consequently, generalizing data from adult to pediatric populations is problematic and requires caution. Ideally, specific data from investigations on children should be used to predict risks in this population.

UNDERSTANDING THE BASICS OF NTCP MODELS

Despite these caveats, model-based risk estimates are a reality. Physicians routinely use models, in their broadest sense, to make treatment decisions. Use of metrics such as the mean lung dose, and cord maximum dose to estimate risks are models, albeit simple ones. We present a primer regarding the basic principles of NTCP models.

Generally, NTCP models attempt to reduce complicated dosimetric and anatomic information to a single risk measure. Most models fall into one of three categories: DVH-reduction models, tissue architecture models, and multiple-metric (*i.e.* multimetric) models.

DVH-reduction models

Although most applications of DVH reduction models are to *nonuniform* dose distributions, they are based on estimated complication probability under *uniform* irradiation. A dose-response for uniform irradiation is described by a mathematical function with at least two parameters: for example TD50, which denotes the dose for 50% complication probability, and *m*, which is inversely proportional to the slope at the

steepest part of the response curve. For a patient cohort with diverse radiosensitivities, the response curve is shallower (larger *m*) than for a biologically similar population receiving the same treatment (14). Various S-shaped functions are used to fit dose-response data, including the probit function used by Lyman (below).

To account for the dose heterogeneity typical of parallel opposed beam irradiation (partial organ uniform irradiation), Jolles (15) described tissue tolerance as a power law of the fractional volume irradiated:

$$D(V_{\text{irradiated}}) = D(V_{\text{reference}}) \left(\frac{(V_{\text{reference}})}{(V_{\text{irradiated}})} \right)^n, \qquad [1]$$

Here $V_{\text{reference}}$ is the reference volume and $V_{\text{irradiated}}$ is the uniformly irradiated volume. *D* is the corresponding tolerance doses, representing a chosen level on the dose–response curve, such as TD50. The parameter *n* controls the volume effect.

Lyman (16) used this power law model to define the risks associated with partial organ volume uniform irradiation. From Eq. 1, decreasing the irradiated volume fraction shifts the dose–response curve (TD50) to higher doses by a factor of the irradiated fractional volume raised to the power ''negative *n*''. The effect of different *n* values on tolerance dose is shown in Fig. 2.

For example, if the *n* parameter equals 1, then the TD50 of irradiation for one half of the volume is expected to increase by a factor of 2, whereas if the *n* parameter is 0.5, TD50 for irradiation of one half the volume would increase by a factor of the square root of 2.

To generalize this to clinically realistic, heterogeneous dose distributions, a summary statistic—the generalized equivalent uniform dose (gEUD)—is often introduced (17, 18). The gEUD is the dose that, if given uniformly to the entire organ, is believed to yield the same complication rate as the true dose distribution. The gEUD is computed by summing over all voxels in the organ:

$$gEUD = \left[\frac{1}{N_{voxels}} (d_1^{1/n} + d_2^{1/n} + \ldots + d_{N_{\text{Voxels}}}^{1/n}) \right]^n. \quad [2]$$

Here N_{Voxels} is the number of equi-volume voxels, and d_i is the dose to the ith voxel. The gEUD equation is consistent with the power-law assumption. Together, the gEUD equation and the Lyman assumptions are often referred to as the Lyman-Kutcher-Burman (LKB) model (16, 18–20).

Note that some analyses use the parameter *n,* and some use the parameter *a,* equal to $1/n$. Both are shown in Fig. 2. When *n* is small (and *a* is large), changes in irradiated volume make only a modest change in relative tolerance whereas, as *n* gets larger (and *a* gets smaller), the tolerance dose depends strongly on the irradiated volume fraction.

Serial vs. parallel complication endpoints

There have been efforts to devise mechanistic models that ascribe the volume dependence of some complications to disruption of the organ's functional architecture by RT (21–23).
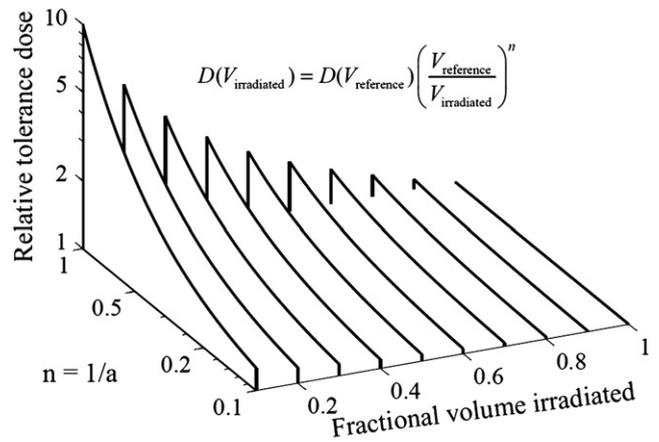

Fig. 2. As the (idealized) irradiated organ fraction decreases, the tolerance dose (*D*) increases, more so for larger values of *n* or smaller values of *a* (=1/*n*). $V_{\text{Reference}}$ represents the reference volume (usually the full organ volume), and $V_{\text{Irradiated}}$ represents the volume irradiated.

In so-called parallel complications, subvolumes of the organ function relatively independently. Sufficiently small portions of the organ can be damaged without clinical effect; the complication is observed only after more than a critical volume is damaged. Parallel complications have large volume effects, and for this reason they are often likened to LKB models with n $\approx$ 1 (as is found in analyses of liver, lung, and kidney complications). More detailed models exist, including models employing the concept of a functional reserve, representing a hypothesized fraction of organ function that can be lost before a complication is likely (23).

In contrast, serial complications occur when even a small portion of the organ suffers damage. Here, *n* is small (*e.g.,* $\approx$ 0.1 for late rectal bleeding). Serial complications are most affected by the hottest portion of the DVH. More detailed models exist for this type of endpoint as well, including models that make explicit the size of small subunits, all of which need to be preserved to avoid a complication (23).

Figure 3 shows how different parts of an example DVH contribute to the overall gEUD as *n* varies. Note that: (a) the lowest value of *n* results in the highest gEUD corresponding to the hottest point on the DVH (more appropriate for serial-like endpoints), and (b) the lower dose bins contribute more when *n* approaches 1 (more appropriate for parallel-like endpoints).

Multimetric models

Clinicians frequently estimate complication risk via a single DVH point based on a statistically significant dose/volume cut-point reported in one or more studies. An example is the often-used V20 (percentage of lung receiving >20 Gy) as a predictor of radiation pneumonitis (24). However, such single ''volume threshold'' rules are overly simple, and often easily manipulated by the treatment planner, or by the optimization software. Optimizing based on such a threshold may introduce a 'kink' in one part of the DVH to achieve a desired ''threshold value,'' while inadequately constraining the rest. An infinite number of very different dose distributions (some likely with very different risks) can have the same V20. The same is true for any
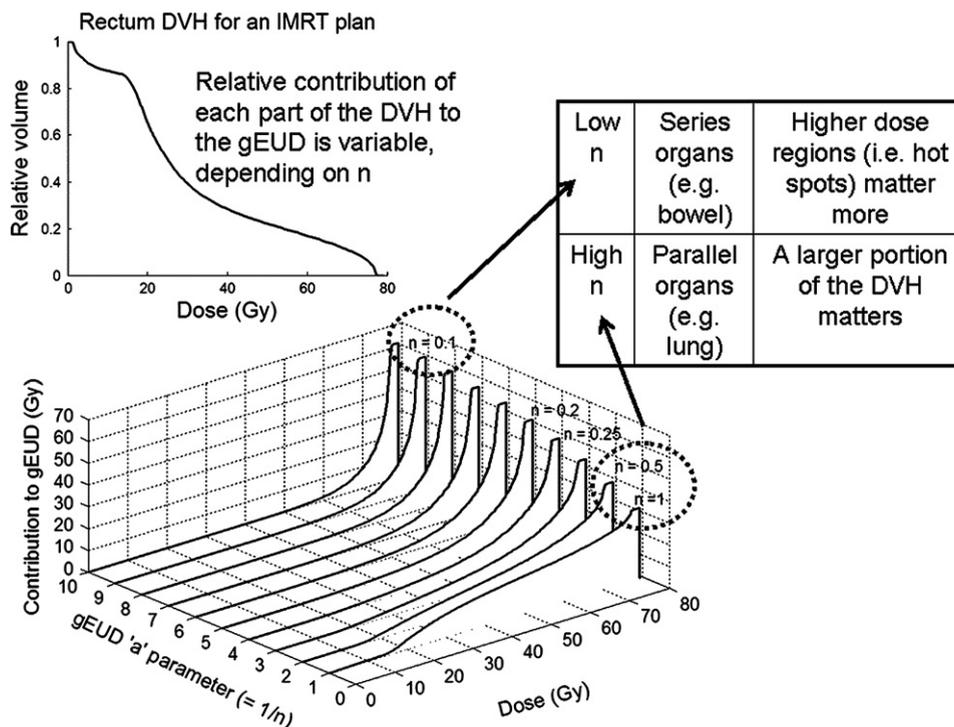
Fig. 3. Volume–effect parameter. The effect of changing the *n* parameter (= $1/a$) in the Lyman model with the generalized equivalent uniform dose equation to compute normal tissue complication probability (NTCP) is shown. Starting with a (real) rectal dose–volume histogram (DVH) computed for an intensity-modulated radiation therapy (IMRT) prostate patient plan (upper left), the DVH is first transformed into a single number by the generalized equivalent uniform dose (gEUD) equation that weights dose values exponentially. Lower figure shows the cumulative contribution of each part of the DVH to the overall gEUD for all bins below the given dose value. As one can see, if *a* is set to 1 (rightmost curve), gEUD would equal the mean dose (*e.g.,* for parallel organs), and many voxels with doses as low as 20 to 30 Gy contribute significantly to the gEUD and therefore may increase the final NTCP value (although contributions are proportional to dose, so higher dose still does contribute more for the same volume). As *n* decreases, the value of gEUD is a determined mainly by the highest dose voxels (*e.g.,* for series organs). Typical clinical values for late rectal bleeding are n ≈ 0.1. Unfortunately, investigators sometimes report *a* (especially when discussing the gEUD) and other-times use *n*, where $n = 1/a$.

DVH-reduction scheme, including the LKB models; markedly different-looking DVHs can yield the same NTCP. However, models that consider a larger fraction of the DVH are less easily manipulated (and may be more radiobiologically logical) than are the threshold models that consider only one point on the DVH. Nonetheless, reports correlating single DVH point thresholds to toxicity are common and are often included in the QUANTEC reviews.

The more robust multimetric approach selects several univariate-significant dosimetric features of the dose distribution (*e.g.,* multiple V_{dose} values) as well as medical variables and use multivariate analysis together with sophisticated statistical methods or ''machine learning'' algorithms to pick out the most significant combinations (25). In-depth discussions of this topic can be found in reviews elsewhere (26–29).

SUMMARY

A major goal of this issue of the *Journal* is to provide practical clinical guidance for physicians and treatment planners. The information presented is not perfect, as evidenced by the multiple caveats above. The lack of good predictors is somewhat unsettling. Nevertheless, the QUANTEC papers present a valuable review. Over time, with the help of new studies

guided by new physical, statistical and biological technologies, we hope to be able to update this information so that patient care can be continually improved.

With the multiple caveats outlined above in mind, a limited summary of available organ-specific dose/volume/outcome data is provided in Table 1. This is not meant to replace the detailed information provided in the individual organ-specific reviews. Treatment planners and physicians are encouraged to read the individual papers to understand the origin, certainty, and nuances that apply to the dose/volume/outcome data provided in the summary table. In general, the dose/volume/outcome data provided in the summary table are associated with generally-regarded clinically acceptable rates of injury; for example, low rates for severe injury (*e.g.,* brain necrosis), and higher rates of less severe endpoints (*e.g.,* erectile dysfunction). Thus, these are dose/volume parameters that might be widely applied in clinical practice. Obviously many clinical situations require treatments that exceed the dose/volume values shown. Where practical, some dose response data are included as well. Furthermore, most of the data in the table is based on conventionally fractionated radiation using conventional techniques, and may or may not be applicable in other settings.

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted)*

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)[†]	Endpoint	Dose (Gy), or dose/volume parameters[†]	Rate (%)	Notes on dose/volume parameters
Brain	Whole organ	3D-CRT	Symptomatic necrosis	Dmax <60	<3	Data at 72 and 90 Gy, extrapolated from BED models
	Whole organ	3D-CRT	Symptomatic necrosis	Dmax = 72	5	
	Whole organ	3D-CRT	Symptomatic necrosis	Dmax = 90	10	
	Whole organ	SRS (single fraction)	Symptomatic necrosis	V12 <5–10 cc	<20	Rapid rise when V12 > 5–10 cc
Brain stem	Whole organ	Whole organ	Permanent cranial neuropathy or necrosis	Dmax <54	<5	
	Whole organ	3D-CRT	Permanent cranial neuropathy or necrosis	D1–10 cc[‖] ≤59	<5	
	Whole organ	3D-CRT	Permanent cranial neuropathy or necrosis	Dmax <64	<5	Point dose <<1 cc
	Whole organ	SRS (single fraction)	Permanent cranial neuropathy or necrosis	Dmax <12.5	<5	For patients with acoustic tumors
Optic nerve / chiasm	Whole organ	3D-CRT	Optic neuropathy	Dmax <55	<3	Given the small size, 3D CRT is often whole organ[‡‡]
	Whole organ	3D-CRT	Optic neuropathy	Dmax 55–60	3–7	
	Whole organ	3D-CRT	Optic neuropathy	Dmax >60	>7-20	
	Whole organ	SRS (single fraction)	Optic neuropathy	Dmax <12	<10	
Spinal cord	Partial organ	3D-CRT	Myelopathy	Dmax = 50	0.2	Including full cord cross-section
	Partial organ	3D-CRT	Myelopathy	Dmax = 60	6	
	Partial organ	3D-CRT	Myelopathy	Dmax = 69	50	
	Partial organ	SRS (single fraction)	Myelopathy	Dmax = 13	1	Partial cord cross-section irradiated
	Partial organ	SRS (hypofraction)	Myelopathy	Dmax = 20	1	3 fractions, partial cord cross-section irradiated
Cochlea	Whole organ	3D-CRT	Sensory neural hearing loss	Mean dose ≤45	<30	Mean dose to cochlear, hearing at 4 kHz
	Whole organ	SRS (single fraction)	Sensory neural hearing loss	Prescription dose ≤14	<25	Serviceable hearing
Parotid	Bilateral whole parotid glands	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <25	<20	For combined parotid glands[¶]
	Unilateral whole parotid gland	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <20	<20	For single parotid gland. At least one parotid gland spared to <20 Gy[¶]

(*Continued*)

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted)* (*Continued*)

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)[†]	Endpoint	Dose (Gy), or dose/volume parameters[†]	Rate (%)	Notes on dose/volume parameters
	Bilateral whole parotid glands	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <39	<50	For combined parotid glands (per Fig. 3 in paper) ¶
Pharynx	Pharyngeal constrictors	Whole organ	Symptomatic dysphagia and aspiration	Mean dose <50	<20	Based on Section B4 in paper
Larynx	Whole organ	3D-CRT	Vocal dysfunction	Dmax <66	<20	With chemotherapy, based on single study (see Section A4.2 in paper)
	Whole organ	3D-CRT	Aspiration	Mean dose <50	<30	With chemotherapy, based on single study (see Fig. 1 in paper)
	Whole organ	3D-CRT	Edema	Mean dose <44	<20	Without chemotherapy, based on single study in patients without larynx cancer**
	Whole organ	3D-CRT	Edema	V50 <27%	<20	
Lung	Whole organ	3D-CRT	Symptomatic pneumonitis	V20 ≤ 30%	<20	For combined lung. Gradual dose response
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 7	5	Excludes purposeful whole lung irradiation
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 13	10	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 20	20	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 24	30	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 27	40	
Esophagus	Whole organ	3D-CRT	Grade ≥3 acute esophagitis	Mean dose <34	5–20	Based on RTOG and several studies
	Whole organ	3D-CRT	Grade ≥2 acute esophagitis	V35 <50%	<30	A variety of alternate threshold doses have been implicated.
	Whole organ	3D-CRT	Grade ≥2 acute esophagitis	V50 <40%	<30	Appears to be a dose/volume response
	Whole organ	3D-CRT	Grade ≥2 acute esophagitis	V70 <20%	<30	
Heart	Pericardium	3D-CRT	Pericarditis	Mean dose <26	<15	Based on single study
	Pericardium	3D-CRT	Pericarditis	V30 <46%	<15	
	Whole organ	3D-CRT	Long-term cardiac mortality	V25 <10%	<1	Overly safe risk estimate based on model predictions

(*Continued*)

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)[†]	Endpoint	Dose (Gy), or dose/volume parameters[†]	Rate (%)	Notes on dose/volume parameters
Liver	Whole liver – GTV	3D-CRT or Whole organ	Classic RILD[††]	Mean dose <30-32	<5	Excluding patients with pre-existing liver disease or hepatocellular carcinoma, as tolerance doses are lower in these patients
	Whole liver – GTV	3D-CRT	Classic RILD	Mean dose <42	<50	
	Whole liver – GTV	3D-CRT or Whole organ	Classic RILD	Mean dose <28	<5	In patients with Child-Pugh A preexisting liver disease or hepatocellular carcinoma, excluding hepatitis B reactivation as an endpoint
	Whole liver – GTV	3D-CRT	Classic RILD	Mean dose <36	<50	
	Whole liver –GTV	SBRT (hypofraction)	Classic RILD	Mean dose <13 <18	<5 <5	3 fractions, for primary liver cancer 6 fractions, for primary liver cancer
	Whole liver – GTV	SBRT (hypofraction)	Classic RILD	Mean dose <15 <20	<5 <5	3 fractions, for liver metastases 6 fractions, for liver metastases
	>700 cc of normal liver	SBRT (hypofraction)	Classic RILD	D_{max} <15	<5	Critical volume based, in 3–5 fractions
Kidney	Bilateral whole kidney[‡]	Bilateral whole organ or 3D-CRT	Clinically relevant renal dysfunction	Mean dose <15–18	<5	
	Bilateral whole kidney[‡]	Bilateral whole organ	Clinically relevant renal dysfunction	Mean dose <28	<50	
	Bilateral whole kidney[‡]	3D-CRT	Clinically relevant renal dysfuntction	V12 <55% V20 <32% V23 <30% V28 <20%	<5	For combined kidney
Stomach	Whole organ	Whole organ	Ulceration	D100[‖] <45	<7	
Small bowel	Individual small bowel loops	3D-CRT	Grade ≥ 3 acute toxicity[§]	V15 <120 cc	<10	Volume based on segmentation of the individual loops of bowel, not the entire potential peritoneal space
	Entire potential space within peritoneal cavity	3D-CRT	Grade ≥ 3 acute toxicity[§]	V45 <195 cc	<10	Volume based on the entire potential space within the peritoneal cavity

(*Continued*)

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted)* (*Continued*)

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)[†]	Endpoint	Dose (Gy), or dose/volume parameters[†]	Rate (%)	Notes on dose/volume parameters
Rectum	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity,	V50 <50%	<15	Prostate cancer treatment
			Grade ≥ 3 late rectal toxicity		<10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity,	V60 <35%	<15	
			Grade ≥ 3 late rectal toxicity		<10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity,	V65 <25%	<15	
			Grade ≥ 3 late rectal toxicity		<10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity,	V70 <20%	<15	
			Grade ≥ 3 late rectal toxicity		<10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity,	V75 <15%	<15	
			Grade ≥ 3 late rectal toxicity		<10	
Bladder	Whole organ	3D-CRT	Grade ≥ 3 late RTOG	Dmax <65	<6	Bladder cancer treatment. Variations in bladder size/shape/location during RT hamper ability to generate accurate data
	Whole organ	3D-CRT	Grade ≥3 late RTOG	V65 ≤50 % V70 ≤35 % V75 ≤25 % V80 ≤15 %		Prostate cancer treatment Based on current RTOG 0415 recommendation
Penile bulb	Whole organ	3D-CRT	Severe erectile dysfunction	Mean dose to 95% of gland <50	<35	
	Whole organ	3D-CRT	Severe erectile dysfunction	D90[‖] <50	<35	
	Whole organ	3D-CRT	Severe erectile dysfunction	D60-70 <70	<55	

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy, SRS = stereotactic radiosurgery, BED = Biologically effective dose, SBRT = stereotactic body radiotherapy, RILD = radiation-induced liver disease, RTOG = Radiation Therapy Oncology Group.

* All data are estimated from the literature summarized in the QUANTEC reviews unless otherwise noted. Clinically, these data should be applied with caution. Clinicians are strongly advised to use the individual QUANTEC articles to check the applicability of these limits to the clinical situation at hand. They largely do not reflect modern IMRT.

[†] All at standard fractionation (*i.e.,* 1.8–2.0 Gy per daily fraction) unless otherwise noted. Vx is the volume of the organ receiving ≥ x Gy. Dmax = Maximum radiation dose.

[‡] Non-TBI.

[§] With combined chemotherapy.

[‖] Dx = minimum dose received by the ''hottest'' x% (or x cc's) of the organ.

[¶] Severe xerostomia is related to additional factors including the doses to the submandibular glands.

** Estimated by Dr. Eisbruch.

[††] Classic Radiation induced liver disease (RILD) involves anicteric hepatomegaly and ascites, typically occurring between 2 weeks and 3 months after therapy. Classic RILD also involves elevated alkaline phosphatase (more than twice the upper limit of normal or baseline value).

[‡‡] For optic nerve, the cases of neuropathy in the 55 to 60 Gy range received ≈59 Gy (see optic nerve paper for details). Excludes patients with pituitary tumors where the tolerance may be reduced.

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