Tolerance of Normal Tissue to Therapeutic Radiation

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Introduction

Radiation therapy is an integral part of the treatment of patients inflicted with cancer. It is estimated that over 60% of patients with cancer will have radiotherapy as part of their total course of treatment [1]. Radiation therapy affects both tumor cells and uninvolved normal cells; the former to the benefit and the later to the detriment of patients. With the goal of achieving uncomplicated local regional control of cancer, balancing between the two is both an art and a science of radiation oncology. Unfortunately, after over 100 years of practicing radiation oncology and in spite of much recent progress, knowledge on either of the two is far from perfect.

From a historical point of view, the first formal attempt to address at least one of the goals, namely normal tissue tolerance to radiation, was carried out by Rubin and Cassarett [2]. Even though this publication was a collection of anecdotal reports, it has served radiation oncologists as a raw reference to build on their own experience.

The decade of the 1980s was a quantum leap of progress in the field of radiation oncology. With the monumental work of researchers on four National Cancer Institute multi-institutional contracts, the science and practice of radiation oncology changed from a two-dimensional (2D) to a three-dimensional (3D)/volumetric process [3]. During the work on these contracts, it became apparent to the clinicians that information on the tumoricidal doses of radiation as well as normal tissue complication doses, especially on partial volumes, is mostly empirical and totally inadequate. A committee was formed to address a part of this dilemma by comprehensively reviewing the available published data. In the process of this review by the committee, it became clear that much of the data is nonexistent and they would have to rely on the collective experience of eight clinicians from major institutions in the United States.

Moreover, in order to shed some light on the volumetric aspect of these issues, it was decided that organs be divided into one-third, two-thirds, and whole organ volumes. In spite of the clear indication in the manuscript on the paucity of solid experimental/prospectively driven data, this publication, so-called Emami's paper, has gained much popularity. The main goal of this publication was to address a clinical need based on available information up to that time and points to the fact that there is a need for extensive and comprehensive research in this area. Obvious limitations of the publication were as follows: [1] It was a literature review up to 1991. [2] It completely pre-dated the 3D-CRTIMRT- IGRT era. Even at that time dose-volume histograms were not in routine clinical use. [3] It was a tabulation of the estimates for three of the aforementioned arbitrary volumes [4]) It was only for external beam radiation with conventional fractionation. [5] Only one severe complication was chosen as an endpoint.

Over the last two decades, since the publication of "Emami's paper" the practice of radiation oncology has been completely revolutionized:

1. Multidisciplinary management of cancer has become the standard of care.

2. Choice of an endpoint for complication analysis and modeling has significantly altered.

3. There has been a major revolutionary change in technology:

a. CT simulation has become routine along with the fusion of other modalities such as MRI, PET, and 4DCT.

b. 3D-CRT/IMRT/IGRT has become standard with the array of evaluation tools.

As a result, dose distributions have become very complex and as of recent, the fourth dimension, namely time, has also been added to this complexity.

Multiplicity and complexities of factors affecting radiation including normal tissue complications have made it impossible to have actual data for every clinical situation facing practicing radiation oncologists. Therefore, there is a need to have reasonable predictive models for plan evaluation, to improve tumor control, and to predict and hopefully prevent normal tissue injury. Optimally, databases on biophysical models should be used in summarizing complicated dose-volume data to help describe clinical outcomes and ultimately aid in the prediction of clinical toxicity.

During the last two decades, a vast amount of published information has become available to address the relationship between dosimetric parameters and the clinical outcomes of normal tissues. Because of different analytic methodologies, calculation methods, endpoints, grading schemes, etc., the data is noisy and sifting through these data for practicing radiation oncologists is a nearly impossible task. Realizing this difficulty and the obvious need for a simplistic format, a group of physicians and researchers were formed with the name "The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC)."

The first goal was to review the available literature of the last 18 years on volumetric/dosimetric information of normal tissue complication and provide a simple set of data to be used by the busy community practitioners of radiation oncology,

Table 1: Variables That Can Impact Normal Tissue Tolerance

I.	Host	Age Comorbid conditions Host response to radiation Smoking KPS	
II	Organ	Pre-radiation organ condition (Poor PFTs; LFTs; COPD) Regional variation of radiosensitivity with the organ Impact of other organs Hierarchal organization of the organ: Serial: dose effect: spinal cord Parallel: volume effect: lung, liver Both: kidney	
III	Natural history of tumor		
IV	Treatment	A—Radiation Dose (max, min, mean) Fractionation (fractional dose): BED Dose rate Overall treatment time Treatment energy Volume (V dose: absolute or relative)	
IV	Treatment	B—Nonradiation Chemotherapy (drug type, dose, schedule) Radiation modifiers (type, dose, schedule) Surgery (interval)	
V	End points ACUTE	Type: Clinical Radiographical: anatomical, functional Biochemical (blood test, functional test) Degree of severity Degree of frequency Impact on quality of life (QOL)	LATE
VI	Issues on reporting of toxicity		

physicists, and dosimetrists. The second goal of the QUANTEC group was to provide reliable predictive models on relationships between dose-volume parameters and the normal tissue complications to be utilized during the planning of radiation oncology. The result of several years of work by this group has recently been published [4–27]. Although these publications contain a comprehensive review of published information and can be a guide for future research on this issue, they still have many shortcomings mainly due to the basic complexity of the subject. This shortcoming has been clearly indicated in the QUANTEC publication and the need for much more data in the future has been emphasized. However, the presented data in the publication is still cumbersome and lacks the "user-friendliness," which is required to be used in the day-to-day practice of a busy community clinician.

As shown in Table.1 there are numerous factors that affect the radiation-induced complications of normal tissues on any given clinical situation. Thus, the experience and judgment of the clinician still plays the most important role in treating patients. As for predictive models, the problem lies in finding a reasonable model, acquiring sufficient data, and applying the statistical methods properly.

So far, in spite of major efforts, there is no model that has been demonstrated to predict radiation responses with sufficient accuracy for widespread clinical use. Most of the modeling at this point is still phenomenological and "descriptive" rather than predictive. The development of reliable and user-friendly predictive models is quite unlikely in the near future.

After reviewing the publication by the QUANTEC group, we attempt to provide the clinicians and the practitioners of radiation oncology a comprehensive but simpler, user-friendly set of data (Tables 2 and 3). It should be noted that the data is not intended to be extrapolated to pediatric patients. The data should be used only as a guide and does not substitute for a physician's clinical judgment. We believe, as indicated in the original paper of "Emami et al." and in the QUANTEC publication, that there is an urgent need for systematic research on this issue, which we hope will be forthcoming.

Word of Caution About BED

Recently, it has become popular (as in many sections of QUANTEC publication) to convert the dose-fractionation to a biological equivalent dose (BED) in order to compare various dosimetric parameters. A practical version of isoeffect formula based on the linear quadratic (LQ) model is:

$$D/Dref\,(/ + dref)/(/ + d) =$$

The index of a/b is calculated based on information from cell survival curves that has been extrapolated and extended to human tumor and normal tissues by some computerized scientists. Unverified assignment of an a/b ratio and using it to calculate a normal tissue tolerance dose can be misleading or at least should be experimentally validated before being recommended for routine clinical use [7,9,10]. The following are some basic facts based on current knowledge:

Fact 1	Dose/fractionation has significant impact on normal tissue complications, e.g., central nervous system (CNS)
Fact 2	1.8–2.0 Gy per fraction, five fractions per week, is considered standard in the United States
Fact 3	In a majority of publications during last two decades an α/β ratio of 2 is used for CNS tissues (28,29)
Fact 4	In the QUANTEC publication an α/β of 3 is used to calculate BED for CNS tissues (7,9)
Fact 5	Using the power of IMRT technology, one can have any dose/fraction as a constraint for tissues such as CNS

The following example depicts the basic fallacies of using BED, calculated from the above formula in clinics. Example:

Gy dose/ fractions	Dose/ fraction (Gy)	α/β for brain tissue	BED
60 Gy/30 Fr[a]	2	1	180
60 Gy/30 Fr[a]	2	2	120
60 Gy/30 Fr[a]	2	3	100

If we arbitrarily choose 1 Gy/fraction/day of brain tissue, then the conversion of BED to dose/ fractionation of 1 Gy/day:

BED	Dose/ fraction (Gy)	α/β	Calculated total dose from formula (Gy)
180	1	1	90
120	1	2	80
100	1	3	75
180	3	1	45
120	3	2	48
100	3	3	51

In the authors' limited informal survey, no radiation oncologists would use 90 Gy at 1 Gy/day or 51 Gy at 3 Gy/day (despite being the same BED as 60 Gy in 30 fractions using an a/b of 1), thus limiting the applicability of BED for routine clinical use. The following descriptive paragraphs of Tables 2 and 3 are presented as general guidelines.

Standard Fractionation

Central Nervous System

Brain

Radiation necrosis of the brain typically occurs 3 months to several years after radiotherapy (median 1–2 years) [3,7].

The original Emami publication estimated a 5% risk of radionecrosis at 5 years with a dose of 60 Gy to one-third of the brain with standard fractionation [3]. More recently, QUANTEC conducted an extensive review of the modern literature and published new dose constraints for the brain [6,7]. The review was based on a heterogeneous group of studies with varied dose and fractionation schemes. Studies were compared using the BED with an a⁄b ratio of 3. A dose–response relationship was found to exist. For standard fractionation, the incidence of radionecrosis appears to be <3% for a dose of <60 Gy. The incidence increases to 5% with a dose of 72 Gy and 10% with a dose of 90 Gy. However, these doses were based on studies with widely varying parameters (target volumes, sample size, brain region, etc.).

It should be noted that an a⁄b ratio of 3 is greater than the values frequently used in the literature and caution should be used when converting to BED (see above discussion). In our practice, we strive to achieve very homogeneous dose distributions with a Dmax (point dose) ≤ 65 Gy with only rare occurrences of symptomatic radiation necrosis.

Brainstem

RT-induced brainstem toxicity can be incapacitating and potentially lethal. The initial estimates by Emami et al. [3]

were of a TD 5/5 of 50 Gy to the entire brainstem and 60 Gy to one-third of the brainstem. These estimates were based on

the scant amount of data in the literature at that time and on clinical experience. The QUANTEC review identified additional modern series focusing on brainstem dose and dosevolume measures [6,9]. The review included series that treated patients with photons, protons, or both. The QUANTEC review concluded that the original Emami constraint of 50 Gy was overly conservative. The entire brainstem can tolerate up to 54 Gy with a <5% risk of brainstem necrosis or neurologic toxicity. Small volumes (1–10 cc) can tolerate up to 59 Gy while a point (<<1 cc) may receive up to 64 Gy.

Spinal Cord

Spinal cord injury due to irradiation, though rare, can be extremely debilitating resulting is paralysis, sensory, deficits, pain, and bowel/bladder incontinence [10,30]. Schultheiss [30] published an extensive review of the literature regarding de novo irradiation of the spinal cord. Among the reviewed studies, a wide range of fractionation regimens were used (2–9 Gy/fraction). An a⁄b ratio of 0.87 was estimated for the spinal cord and corresponding 2-Gy equivalent doses were calculated. The review estimated the risk of myelopathy to be 0.2% at 50 Gy and 5% at 59.3 Gy.

Similar conclusions regarding a⁄b ratio and dose-volume limits were published by QUANTEC [6,10]. It should be noted that an a⁄b ratio of 0.87 is less than the values frequently used in the literature and caution should be used when converting to BED (see above discussion).

Chiasm and Optic Nerves

Radiation-induced optic neuropathy (RION) is infrequent but usually results in rapid painless visual loss [8].

The initial Emami review listed a TD 5/5 of 50 Gy to the whole organ without partial volume tolerance data [3].

Again, this was based primarily on clinical experience and sparse published data. Many more studies are now published and were reviewed by QUANTEC [6,8]. Based on the QUANTEC review, a

Table 2: Normal Tissue Tolerance for Standard Fractionation

Organ	Endpoint	Rate (%)	Dose-volume parameter	D_{max} (Gy)	D_{mean} (Gy)
Brain	Symptomatic necrosis	<3 <5		<60 <65	
Brainstem	Necrosis or cranial neuropathy	<5 <5	D100 <54 Gy D1–10 cc ≤59 Gy	<64 Point	
Spinal cord	Grade ≥2 myelopathy	<1		50	
Optic nerve & chiasm	Optic neuropathy	<3 3–7		<55 55–60	<50
Retina	Blindness	<1		<50	
Cochlea	Hearing loss	<15			≤45
Parotid 1	Grade 4 xerostomia	<20			<20
Parotid 2		<20			<25
Mandible	ORN	<5		<70 Point	
Pharyngeal constrictors	PEG tube dependent Aspiration	<5 <5			<50 <60
Larynx	Grade ≥2 edema	<20	V50 <27%		<44
Brachial plexus	Clinically apparent nerve damage	<5		<60	
Lung	Symptomatic pneumonitis	5 10 20 30 40	V5 <42%, V20 <22% V20 <31% V20 <40%		7 13 20 24 27
Esophagus	Grade ≥2 esophagitis Grade ≥3 esophagitis	<30 ≤10	V35 <50% V50 <40% V70 <20% V60 <30%	<74 Point	<34
Heart	Pericarditis Long-term cardiac mortality	<15 <1	V30 <46% V25 <10%		<26
Liver	RILD, normal liver RILD, liver disease	<5 <5			≤30 ≤28
Kidney 1	Renal dysfunction	<5	Equivalent of 1 kidney <18 Gy		
Kidney 2	Renal dysfunction	<5			<18
Stomach	Ulceration		D100 <50 Gy		
Small Bowel	Acute grade ≥3 toxicity Late obstruction/perforation	<10 <5	V15 <120 cc V50 <5%		
Rectum	Grade ≥2/≥3 late toxicity Grade ≥2/≥3 late toxicity Grade ≥2/≥3 late toxicity Grade ≥2/≥3 late toxicity Grade ≥2/≥3 late toxicity	<10/<15 <10/<15 <10/<15 <10/<15 <10/<15	V50 <50% V60 <35% V65 <25% V70 <20% V75 <15%		
Bladder	Grade ≥3 late toxicity	<6 ?	D100 <65 Gy V65 ≤50% V70 ≤35% V75 ≤25% V80 ≤15%		
Penile bulb	Severe erectile dysfunction	<35			<50
Femoral head	Necrosis	<5	D100 <52 Gy		

Parotid 1, sparing single parotid gland; Parotid 2, combined parotid glands; Kidney 1, bilateral partial kidney RT; Kidney 2, bilateral whole kidneys; Vx, volume of the organ receiving ≥x Gy; Dx, minimum dose received by x% of the organ; D_{max}, maximum radiation dose; D_{mean}, mean radiation dose.

Table 3:Mostly Unvalidated Normal Tissue Dose Constraints for SBRT

Serial tissue	Volume (mL)	Volume max (Gy)	Max point dose (Gy)	Endpoint (≥grade 3)
Single-fraction treatment				
Brain	5–10	12[a]		Necrosis {<20%}
Optic pathway	<0.2	8	10 12	Neuritis Neuritis {<10%}
Cochlea			12 ≤14[a]	Hearing loss Hearing loss {<25%}
Brainstem	<1	10	15 <12.5[a]	Cranial neuropathy Cranial neuropathy {<5%}
Spinal cord	<0.25 <1.2	10 7	14 13[a]	Myelitis Myelitis {<1%}
Cauda equina	<5	14	16	Neuritis
Sacral Plexus	<3	14.4	16	Neuropathy
Esophagus	<5	14.5	19	Stenosis/fistula
Ipsilateral brachial plexus	<3	14.4	16	Neuropathy
Heart/pericardium	<15	16	22	Pericarditis
Great vessels	<10	31	37	Aneurysm
Trachea and ipsilateral bronchus	<4	8.8	22	Stenosis/fistula
Skin	<10	14.4	16	Ulceration
Stomach	<10	13	16	Ulceration/fistula
Duodenum	<5	8.8	16	Ulceration
Jejunum/ileum	<5	9.8	19	Enteritis/obstruction
Colon	<20	11	22	Colitis/fistula
Rectum	<20	11	22	Proctitis/fistula
Bladder wall	<15	8.7	22	Cystitis/fistula
Penile bulb	<3	14	34	Impotence
Femoral heads (right and left)	<10	14		Necrosis
Renal hilum/vascular trunk	<2/3 volume	10.6		Malignant hypertension

Parallel tissue	Critical volume (mL)	Critical volume dose max (Gy)	Endpoint (≥grade 3)
Lung (right and left)	1,500	7	Basic lung function
Lung (right and left)	1,000	7.4	Pneumonitis
Liver	700	9.1	Basic liver function
Renal cortex (right and left)	200	8.4	Basic renal function

Three-fraction treatment				
Optic pathway	<0.2	15 (5 Gy/fx)	19.5 (6.5 Gy/fx)	Neuritis
Cochlea			20 (6.67 Gy/fx)	Hearing loss
Brainstem	<1	18 (6 Gy/fx)	23 (7.67 Gy/fx)	Cranial neuropathy
Spinal cord	<0.25 <1.2	18 (6 Gy/fx) 11.1 (3.7 Gy/fx)	23 (7.67 Gy/fx)	Myelitis
Cauda equine	<5	21.9 (7.3 Gy/fx)	24 (8 Gy/fx)	Neuritis
Sacral Plexus	<3	22.5 (7.5 Gy/fx)	24 (8 Gy/fx)	Neuropathy
Esophagus	<5	21 (7 Gy/fx)	27 (9 Gy/fx)	Stenosis/fistula
Ipsilateral brachial plexus	<3	22.5 (7.5 Gy/fx)	24 (8 Gy/fx)	Neuropathy
Heart/pericardium	<15	24 (8 Gy/fx)	30 (10 Gy/fx)	Pericarditis
Great vessels	<10	39 (13 Gy/fx)	45 (15 Gy/fx)	Aneurysm
Trachea and ipsilateral bronchus	<4	15 (5 Gy/fx)	30 (10 Gy/fx)	Stenosis/fistula
Skin	<10	22.5 (7.5 Gy/fx)	24 (8 Gy/fx)	Ulceration
Stomach	<10	21 (7 Gy/fx)	24 (8 Gy/fx)	Ulceration/fistula
Duodenum	<5	15 (5 Gy/fx)	24 (8 Gy/fx)	Ulceration
Jejunum/ileum	<5	16.2 (5.4 Gy/fx)	27 (9 Gy/fx)	Enteritis/obstruction
Colon	<20	20.4 (6.8 Gy/fx)	30 (10 Gy/fx)	Colitis/fistula
Rectum	<20	20.4 (6.8 Gy/fx)	30 (10 Gy/fx)	Proctitis/fistula
Bladder wall	<15	15 (5 Gy/fx)	30 (10 Gy/fx)	Cystitis/fistula
Penile bulb	<3	21.9 (7.3 Gy/fx)	42 (14 Gy/fx)	Impotence
Femoral heads (right and left)	<10	21.9 (7.3 Gy/fx)		Necrosis
Renal hilum/vascular trunk	<2/3 volume	18.6 (6.2 Gy/fx)		Malignant hypertension

Parallel tissue	Critical volume (mL)	Critical volume dose max (Gy)	Endpoint (≥grade 3)
Lung (right and left)	1,500	10.5 (3.5 Gy/fx)	Basic lung function
Lung (right and left)	1,000	11.4 (3.8 Gy/fx)	Pneumonitis
Liver	700	17.1 (5.7 Gy/fx)	Basic liver function
Renal cortex (right and left)	200	14.4 (4.8 Gy/fx)	Basic renal function

Table 3: Mostly Unvalidated Normal Tissue Dose Constraints for SBRT (Continued)

Serial tissue	Volume (mL)	Volume max (Gy)	Max point dose (Gy)	Endpoint (≥grade 3)
Five-fraction treatment				
Optic pathway	<0.2	20 (4 Gy/fx)	25 (5 Gy/fx)	Neuritis
Cochlea			27.5 (5.5 Gy/fx)	Hearing loss
Brainstem	<1	26 (5.2 Gy/fx)	31 (6.2 Gy/fx)	Cranial neuropathy
Spinal cord	<0.25 <1.2	22.5 (4.5 Gy/fx) 13.5 (2.7 Gy/fx)	30 (6 Gy/fx)	Myelitis
Cauda equine	<5	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Neuritis
Sacral Plexus	<3	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Neuropathy
Esophagus	<5	27.5 (5.5 Gy/fx)	35 (7 Gy/fx)	Stenosis/fistula
Ipsilateral brachial plexus	<3	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Neuropathy
Heart/pericardium	<15	32 (6.4 Gy/fx)	38 (7.6 Gy/fx)	Pericarditis
Great vessels	<10	47 (9.4 Gy/fx)		Aneurysm
Trachea and ipsilateral bronchus	<4	18 (3.6 Gy/fx)	38 (7.6 Gy/fx)	Stenosis/fistula
Skin	<10	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration
Stomach	<10	28 (5.6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration/fistula
Duodenum	<5	18 (3.6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration
Jejunum/ileum	<5	19.5 (3.9 Gy/fx)	35 (7 Gy/fx)	Enteritis/obstruction
Colon	<20	25 (5 Gy/fx)	38 (7.6 Gy/fx)	Colitis/fistula
Rectum	<20	25 (5 Gy/fx)	38 (7.6 Gy/fx)	Proctitis/fistula
Bladder wall	<15	18.3 (3.65 Gy/fx)	38 (7.6 Gy/fx)	Cystitis/fistula
Penile bulb	<3	30 (6 Gy/fx)	50 (10 Gy/fx)	Impotence
Femoral heads (right and left)	<10	30 (6 Gy/fx)		Necrosis
Renal hilum/vascular trunk	<2/3 volume	23 (4.6 Gy/fx)		Malignant hypertension
Parallel tissue	**Critical volume (mL)**	**Critical volume dose max (Gy)**		**Endpoint (≥grade 3)**
Lung (right and left)	1,500	12.5 (2.5 Gy/fx)		Basic lung function
Lung (right and left)	1,000	13.5 (2.7 Gy/fx)		Pneumonitis
Liver	700	21 (4.2 Gy/fx)		Basic liver function
Renal cortex (right and left)	200	17.5 (3.5 Gy/fx)		Basic renal function

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[a]Data from QUANTEC (3).
{} rate of endpoint.

whole organ dose of 50 Gy is associated with <1% risk of blindness. In fact, blindness was quite rare until a dose of ≥55 Gy. Between 55 and 60 Gy, the risk of blindness is approximately 3% to 7%. At doses >60 Gy, the risk of RION greatly increases.

Head and Neck

Retina

Radiation retinopathy, resulting in loss of vision or visual acuity, presents similarly to diabetic retinopathy often within 5 years of radiotherapy. Parsons [31,32] reported only one instance of retinopathy with a dose <50 Gy to at least half the posterior pole of the eye with a steep dose–response curve at doses >50 Gy. Subsequently, Parsons [33] demonstrated no cases of retinopathy at doses below 45 Gy but a steep dose curve at doses >45 Gy. More recently, Monroe et al. reported a 4% rate of retinopathy after <50 Gy was received by at least 25% of the globe with conventional fractionation and modern conformal techniques [34]. Using hyperfractionation, the rate of retinopathy decreased from 37% to 13% with doses ≥50 Gy. Takeda et al. reported no cases of retinal complications when the Dmax was <50 Gy [35]. Clearly, the dose tolerance of the retina is dependent upon multiple factors including predisposing comorbidities, the fractionation schema employed, and the volume that is irradiated. Multiple publications have demonstrated a steep dose–response curve for doses >50 Gy [33–35]. Using modern treatment planning techniques and standard fractionation, we recommend limiting the retina to a Dmax <50 Gy.

Cochlea

Damage to the cochlea may result in sensorineural hearing loss (SNHL). As summarized by QUANTEC, high frequency hearing loss is much more common than lowfrequency hearing loss [11]. Cisplatin-based chemotherapy can have an additional adverse effect on SNHL. The definition

of clinically significant SNHL varies throughout the literature but is generally considered to be an increase in bone conduction threshold of 10 to 30 dB. The QUANTEC review examined several series and suggested a mean dose constraint of ≤45 Gy [6,11]. Chan et al. conducted a longitudinal study of 87 consecutive patients treated for nasopharyngeal carcinoma, mostly treated with cisplatin-based chemoradiotherapy [36]. A mean dose of ≤47 Gy to the cochlea resulted in <15% rate of SNHL. Therefore, based on a review of the literature with modern treatment planning techniques and concurrent cisplatin chemoradiotherapy we believe that a cochlear mean dose constraint of ≤45 Gy will result in a <15% rate of SNHL.

Parotid

Late salivary dysfunction is a common toxicity from radiotherapy for head and neck cancer that can take up to Late salivary dysfunction is a common toxicity from radiotherapy for head and neck cancer that can take up to 2 years to recover (37,38). Xerostomia has been widely defined in the literature from patient-reported outcomes to objective salivary flow. Quantifiably, xerostomia is defined by the LENT-SOMA scale. Grade 4 xerostomia consists of an objective reduction of ≥75% of baseline salivary function. The QUANTEC review [6,12] summarized the literature including the Washington University experience [37]. Blanco demonstrated that sparing (mean dose <20 Gy) of at least one parotid gland minimized the incidence grade 4 xerostomia. Likewise, limiting both parotids to a mean dose of <25 Gy resulted in minimal grade 4 xerostomia. Dose to the parotids should be reduced as much as clinically allowable as lower mean doses generally result in better salivary function [12].

Mandible

The rates of osteoradionecrosis (ORN) of the mandible have decreased over the past few decades [39]. The risk of ORN is dependent on several factors including radiation dose, use of chemotherapy, dental hygiene, tumor location, mandibular surgery, and radiation technique [39–44]. Ben-David et al. [40] demonstrated a steep dose falloff across the mandible when IMRT is employed. In their study, ≥50% of the patients in their study received ≥70 Gy to ≥1% of the mandibular volume with no cases of grade ≥2 ORN. Additional studies, including IMRT for oral cavity cancers, demonstrate a rate of ORN near 5% [41–43]. Therefore, we recommend limiting the mandible to a Dmax (point dose) ≤70 Gy when using IMRT.

Pharyngeal Constrictors

Treatment intensification for head and neck cancer has resulted in an increased rate of late sequela including dysphagia and aspiration. Modern treatment planning has allowed the study of various components of the swallowing apparatus. The results in the literature in this burgeoning area of research are variable as summarized in the QUANTEC review [6,13]. Several groups have found the dose to the superior and/or middle pharyngeal constrictor muscles to be of paramount importance. Others have demonstrated the dose to the inferior pharyngeal constrictors or larynx to be of importance. Feng et al. [45] found no patients to have aspiration when the pharyngeal constrictors were limited to a mean dose of <60 Gy. We base our practice primarily on the findings from the University of Michigan and limit the superior pharyngeal constrictors to a mean dose of <60 Gy whenever clinically possible.

Larynx

Toxicity from radiotherapy to the larynx can include vocal dysfunction and laryngeal edema. The original Emami publication [3] addressed the risk of cartilage necrosis; however, this is rarely seen in modern radiotherapy and is not as relevant of an endpoint as vocal function and laryngeal edema. The QUANTEC publication reviewed several studies involving vocal dysfunction, concluding doses to multiple structures (e.g., larynx, pharynx, and oral cavity) play an important role in voice function [6,13]. Radiotherapy is commonly used for treatment of early-stage glottic cancer, employing doses >60 Gy, with a good voice outcome. A single publication (46) on laryngeal edema was reviewed, which found <20% incidence of ≥grade 2 edema when the mean laryngeal dose was <43.5 Gy and the V50 <27%.

Thorax

Brachial Plexus

Brachial plexopathy can manifest as pain, paresthesias, or motor deficits of the upper

extremity [47]. Muscular atrophy and edema may develop. Emami et al. [3] suggested that the TD 5/5 to the entire brachial plexus was 60 Gy. More recently, several studies with over 20 years of followup have suggested that the incidence of brachial plexopathy continues to rise after 5 years and may not be apparent for up to 20 years after radiotherapy [47,48]. The brachial plexus appears to be especially sensitive to fractionation schedules, with the risk of injury much higher for larger fractions despite equivalent BED [49]. With standard fractionation the risk of clinically apparent nerve damage seems to be <5%, after 5 years of completing radiotherapy, when the brachial plexus is limited to 60 Gy.

Lung

Symptomatic radiation pneumonitis (RP) is one of the most common toxicities in patients treated with radiation for cancers of the lung, breast, and mediastinal lymphatics. The risk of RP often limits the dose delivered for treatment of these malignancies. Since the initial Emami publication (3) there has been an extensive amount of research attempting to relate many different dose-volume parameters to RP. The QUANTEC publication reviewed >70 published articles looking at both mean lung doses and Vx parameters [6,14]). This comprehensive review demonstrated no clear threshold dose for symptomatic RP. The compiled data showed a mean dose–response curve with a 20% risk of RP for a mean lung dose of 20 Gy. In addition, multiple Vx values have been investigated for predicting RP but the data are not as consistent as the data for mean lung doses. Using 3D techniques, Graham found the V20 to be the most useful parameter for predicting the risk of RP [50]. When Vx values are used, the V20 is the most commonly incorporated parameter.

Esophagus

Acute esophagitis commonly occurs during radiotherapy for thoracic malignancies and can lead to hospitalizations, procedures, and treatment breaks [16]. Most series in the literature report rates of RTOG grade ≥2 esophagitis. The QUANTEC review summarized 11 studies that used 3D treatment planning [6,16]. A single best parameter was not identified due to the diverse range of dose-volume metrics that correlated with acute esophagitis [51–53]. As demonstrated in the QUANTEC publication, there appears to be a trend demonstrating increased rates of acute esophagitis for volumes receiving >40 to 50 Gy. Currently, the ongoing RTOG 0617 is collecting V60 data on all patients and recommends keeping the mean dose <34 Gy [54].

Heart

Clinical pericarditis and long-term cardiac mortality are the two most relevant cardiac toxicities. Since the original Emami publication (3), there remains a paucity of data reporting rates of pericarditis with dose-volume parameters. Indeed, several current RTOG protocols continue to use constraints similar to the original Emami TD 5/5 dose-volume estimates for the heart [54–56]. As reviewed by QUANTEC [6,15], two esophageal cancer studies [57,58] assessed 3D-derived data with both studies demonstrating a rate of pericarditis <15% when the mean pericardial dose was <26 Gy. In addition, Wei found the pericardial V30 <46% to be significant on multivariate analysis. Long-term cardiac mortality has been demonstrated in multiple studies, most commonly in the treatment of breast cancer and Hodgkin's lymphoma [15]. A joint analysis of the Hodgkin's and breast cancer data [59,60], summarized by QUANTEC, produced a dose–response curve for cardiac mortality. QUANTEC proposed a conservative approach, predicting that a V25 <10% of the heart will be associated with a <1% probability of cardiac mortality at 15 years after radiotherapy.

Abdomen

Liver

Radiation-induced liver disease (RILD) typically occurs between 2 weeks and 3 months after radiotherapy. Preexisting liver disease may render patients more susceptible to RILD [17]. The findings by QUANTEC [6,17] are very similar to the original estimates by Emami et al. [3], suggesting a <5% rate of RILD when the mean liver dose is ≤30 Gy in patients without preexisting liver disease or primary liver cancer. The mean liver dose should be ≤28 Gy in those patients with preexisting liver disease.

Kidney

Radiation-induced renal dysfunction can be expressed in various ways including symptomatic

expression, biochemical changes, or radiologic findings. As summarized by QUANTEC, a wide array of endpoints has been used in the literature from a decrease in creatinine clearance to renal failure (6,19). For bilateral whole kidney irradiation, a pooled analysis by Cassady [61] concluded a mean dose of 18 Gy corresponded to a 5% risk of injury at 5 years. For bilateral partial kidney irradiation, the data is less clear with a multitude of dose-volume metrics studied by several investigators [19]. Small volumes of the kidney can tolerate relatively high doses of radiation. QUANTEC estimated a <5% risk of injury when the mean kidney dose is limited to <18 Gy. In addition, the current common practice of limiting the equivalent of one kidney to <20 Gy seems to be reasonable and is frequently used in our practice.

Stomach

Late radiation-induced toxicity to the stomach can include dyspepsia and ulceration. Since the original Emami publication [3], few studies have reported severe RT-related gastric toxicity. The QUANTEC publication reviewed these studies, primarily pancreatic cancer trials, and concluded that a whole organ dose of 50 Gy has been associated with a 2% to 6% risk of severe late toxicity [6,18] (similar to Emami et al.).

Small Bowel

Small-bowel toxicity can be greatly affected by the use of concurrent chemotherapy and prior abdominal surgery. In particular, concurrent chemotherapy can impact the rates of acute small-bowel toxicity. Modern series employing 3D-conformal RT or IMRT have demonstrated that the volume of small bowel receiving relatively low doses of radiation plays a significant role in the rate of acute toxicity [18]. When contouring individual bowel loops, the most robust dose-volume metric is the V15. The rate of grade ≥3 acute toxicity is <10% when the V15 <120 cc [62,63]. When the entire potential space within the peritoneal cavity is contoured, a V45 <195 cc results in <10% acute toxicity [64]. Late small-bowel toxicity, consisting of obstruction or perforation, can be influenced by prior abdominal surgery. Modern series reviewed by QUANTEC generally confirm the Emami et al. [3] TD5/5 estimate for partial organ irradiation [6,18]. In practice, we limit the volume of the small bowel receiving 50 Gy to much less than one-third. We generally limit the V50 <5% based on the clinical scenario.

Pelvis

Rectum

The treatment of prostate cancer has evolved such that the

great majority of patients will be alive for many years after radiotherapy. Late rectal toxicities from radiotherapy can significantly impact quality of life (QOL). Since Emami et al. [3], numerous studies have employed dose escalation using 3D-CRT or IMRT for the treatment of prostate cancer. These trials have resulted in the publication of many dose-volume analyses as summarized by the QUANTEC review [6,21]. The dose-volume results are surprisingly consistent suggesting that high doses are most important in determining risk of toxicity.

Bladder

The bladder frequently receives radiation during the treatment of commonly encountered pelvic malignancies such as prostate, cervical, and bladder cancer. Due to the distensibility of the bladder it is difficult to conduct robust dose-volume analyses. The QUANTEC publication was unable to find any reliable data for partial bladder volume constraints in the treatment of prostate cancer and recommended using RTOG 0415 dose limits (6,20,65). In the treatment of bladder cancer, where the entire organ is targeted, rates of severe late bladder toxicity are varied (20). Shipley et al. (66) reported the pooled results of multiple RTOG trials demonstrating a grade ≥3 toxicity rate of ≤6% when treating the bladder to a dose of 64 to 65 Gy.

Penile Bulb

Erectile dysfunction can have a significant detrimental effect on QOL after treatment for prostate cancer. QUANTEC summarized the published studies correlating the dose and volume of the penile bulb that is irradiated with rates of erectile dysfunction [22]. The results for various dosevolume parameters are conflicting. There is some data to support limiting the D70 <70 Gy and D90 <50 Gy. However, the strongest data supports the recommendation of limiting the penile bulb to a mean dose of <52 Gy without compromising target coverage [67].

Femoral Head

Toxicity of radiation treatment to the pelvis includes femoral head necrosis, femoral neck fracture, or long-term sequela resulting in hip replacement surgery. Besides radiation dose and volume, additional risk factors may include preexisting osteoporosis/osteopenia and androgen deprivation therapy [68–70]. Emami et al. [3] suggested a TD 5/5 of 52 Gy to the whole femoral head. Grigsby et al. published the Washington University experience and documented a 4.8% incidence of femoral neck fracture following groin irradiation [68]. Of note, there was only one case of femoral neck fracture when the whole femoral neck received ≤50 Gy. There is0 little data describing femoral toxicity when higher doses are delivered to small volumes of the femoral head or neck [71–74]. We generally limit the entire femoral head to <50 Gy in an attempt to limit femoral head/neck toxicity to <<5%.

Hypofractionation

Some of the earliest radiotherapy treatments were delivered in a hypofractionated fashion. As technology and radiobiology advanced, protracted fractionation schemes became the norm. Eventually, hypofractionation was again pursued and used to treat intracranial lesions. Stereotactic radiosurgery (SRS) has been used for decades and its success led to the use of hypofractionated treatment outside the brain. Over the past 15 years, the use of stereotactic body radiotherapy (SBRT) has become widespread and utilized to treat a number of cancers. The QUANTEC group reviewed the literature pertaining to SRS and published tolerance doses for some CNS organs at risk [6–11]. The most comprehensive review to date was published by Timmerman [75]. Both intracranial and extracranial organ tolerances were reviewed and adjusted for either single-fraction, three-fraction, or five-fraction treatments. Because the data in this burgeoning modality is relatively limited, the dose constraints are not validated. Rather, they are based on a combination of published data, clinical observations, modeling, and educated guessing. Despite these caveats, the dose constraints published by Timmerman provide an excellent starting point for clinical use.

Conclusion

From the pioneering work of Rubin and Cassarett, to the monumental work by Emami et al. and now the exhaustive review by QUANTEC, great progress has been made in the field of normal tissue tolerance to therapeutic radiation. Despite these efforts, many questions still remain. Normal tissue tolerance is an extremely complex issue and multifactorial in nature. There continues to be an urgent need for comprehensive and collaborative research. The dose-volume parameters within this chapter should be used only as a guide. For instance, there are clinical scenarios where a 5% rate of a particular toxicity is unacceptable. In contrast, there may be cases where one is willing to accept the risk a 20% rate of a particular side effect in order to obtain a desired clinical outcome. Therefore, it is imperative that the clinical judgment of the treating physician prevails in the treatment decision-making process.

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