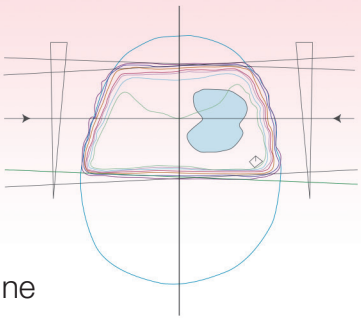
CHAPTER

14 Late Effects after Radiation



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INTRODUCTION AND GENERAL CONSIDERATIONS

Statement of the Problem

Incidental irradiation of normal tissues is unavoidable during radiation therapy. Predicting the risk of radiation-induced injury is challenging. The primary determinants of injury are the radiation dose (total dose and dose per fraction) and the volume of normal tissue irradiated. Additional treatment factors that influence risk include dose rate, overall treatment time, treatment energy, the use of concurrent chemotherapy, radiation protectors, or other biological modifiers, and the interval between radiation courses in patients undergoing a second course of radiation. Host-related factors include comorbid conditions (e.g., diabetes, collagen vascular disease), inherent radiation sensitivity (e.g., underlying genetics), and patient age. Organ related variables include preradiation organ compromise or loss, development of severe acute toxicity (resulting in consequential late effects), regional variation of radiosensitivity within an organ, and hierarchal organization of the organ (i.e., whether damage to a portion of the organ affects only that portion or has more widespread effect). Furthermore, an organ may have more than one type of late toxicity that may or may not have different tolerance doses. Tumors can infiltrate into normal tissues, either at presentation or after treatment (i.e., local failure), compromising organ function and leading to late sequelae.

What Are the Target Cells/Tissues for Radiation-Associated Normal Tissue Injury?

Different organs have different dose/volume thresholds for the development of radiation-associated injury. The critical question arising from this observation is: what are the dose-sensitive targets in normal tissues resulting in late toxicity. Damage to either the functional (parenchymal) or stromal cells of the organ, or the fine vasculature, have been implicated. Differences in radiation susceptibility of different organs may therefore be as a result of different sensitivities of these functional cells, regional variation in the susceptibilities of small vessels because of the stroma or microenvironment, different capacities for neo-vascularization, or differences in the redundancy of the blood flow (i.e., those tissues relying on fewer vessels may be more susceptible to radiation damage), or functional reserve.

Utility and Limitations of Dose-Volume Histograms

The focus of this chapter will be on the review of credible data associating radiation dose/volume parameters with the risk of normal tissue injury. Three-dimensional (3D) planning has become standard practice, allowing the radiation oncologist to quantitate doses to normal tissues in the region of interest. 3D dose/volume data can be difficult for clinicians to easily comprehend because the distributions are two dimensional (2D). Visualizing isodose distributions is challenging and comparing competing distributions is largely subjective. Therefore, dose-volume histograms (DVHs; essentially 2D representations of the 3D data) were embraced as a rapid way to summarize the dose distribution. A DVH is generated by tallying the doses delivered to each (or a representative sample of) voxel of tissue and represents that information as a cumulative histogram of dose (x-axis) and volume (y-axis). Each point along the histogram represents the volume of that organ receiving more than or equal to that dose (e.g., V20 is the volume of an organ receiving at least 20 Gy). A DVH can be readily visualized and provides a quick and easy way to describe the dose/volume characteristics of the 3D dose distribution. However, a DVH achieves this by discarding all spatial information and the DVH does not account for variations in fraction size. Functional and structural complexities, and spatial variations in function or sensitivity, are thus not considered in DVHs. Possible interactions between organs are also not considered with this construct.

Despite the marked data reduction in going from a 3D plan to a DVH, DVHs also remain challenging for clinicians to consider and compare because of the previously mentioned issues relating to functional heterogeneity but also incomplete knowledge about radiation sensitivity of tissues. Therefore, it has become attractive to further data reduce and extract "figures of merit" from the DVH. The critical metrics that will considered in this review are the mean organ dose and discrete points on the DVH. These include (Figure 14-1):

1. *Vx* reflects the volume of tissue (generally a percentage) receiving ≥*X* Gy. This is probably the most commonly used metric for parallel-type organs such as the lung and kidney. For these, as discussed, the portions of the organ exposed to a "regionally injuring" dose of radiation will become dysfunctional. Thus, the percentage of the organ exposed to that dose is a useful parameter.
2. *Dx* reflects the minimum dose to the hottest *x*% (generally percentage of total volume) of tissue. This parameter is not widely used clinically. It might be most useful for parallel-type organs where the percentage of an organ's function that can be lost is known (e.g., let's say 30%). Then, if the D30 is less than the locally injuring dose, global organ function should remain. Similarly, for organs where an injury might be clinically manifest if there is a hot spot of a particular size, the *Dx*, where *x* is equal to that critical size, might be a useful parameter to predict outcomes.
3. *Dmax* is the maximum dose delivered to an organ and is most useful for series organs. *Dmax* is analogous to *Dx* as the volume *x* decreases toward zero.
4. Mean dose is the simple arithmetic average of the dose to an organ. For parallel organs where there is a gradual dose-response function for radiation-induced regional injury, the mean dose might reasonably correlate with outcomes.

More complex modeling has also been widely used to extract figures of merit that better reflect the entire DVH, rather than a single point (e.g., *Dmax, Dx, Vx*). These models will "sum up" the risk associated with each component of a DVH and apply different methods of summing, depending on the type (or architecture/structure) of the organ. For example, for a series-structured organ, the high-dose region of the DVH

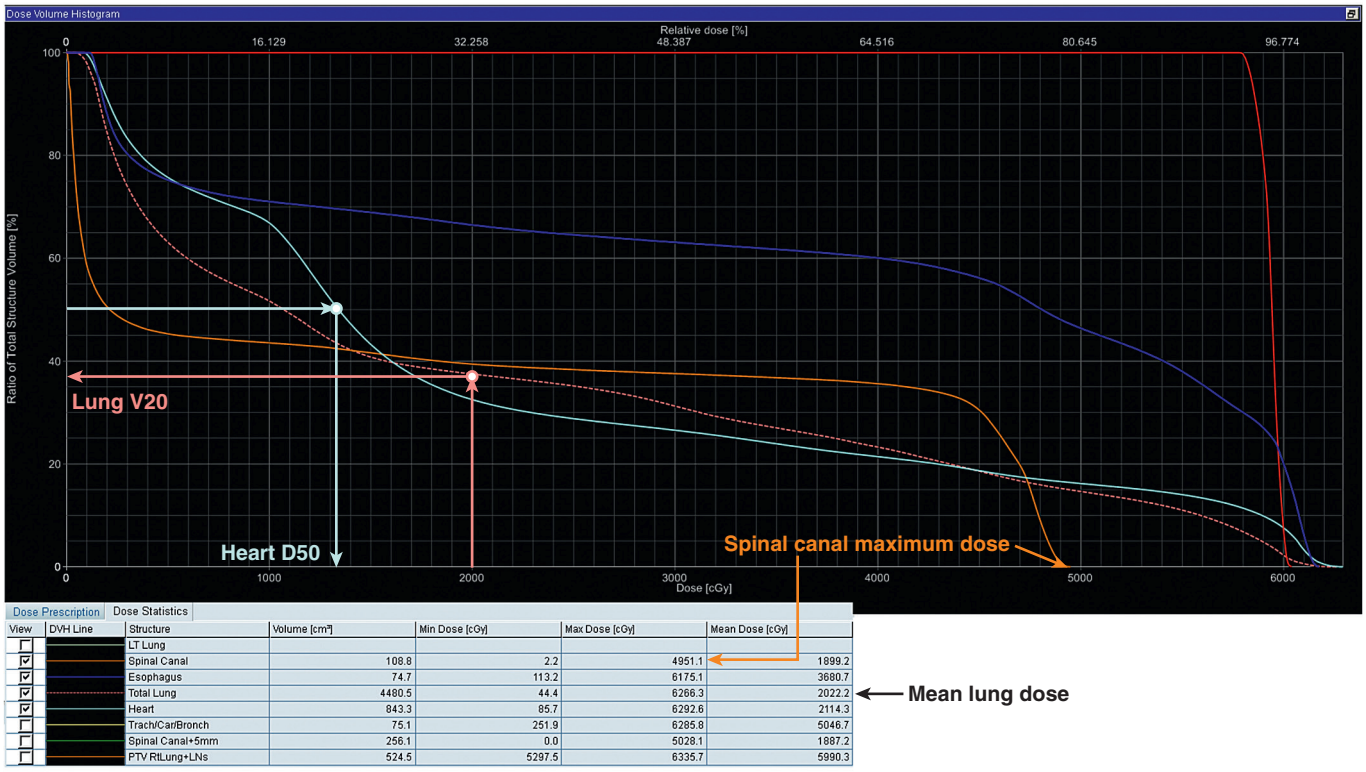

Figure 14-1 Illustration of *Vx*, *Dx*, and *Dmax*. Mean organ dose is calculated by averaging the dose to each voxel of a tissue and is generally calculated by the treatment planning software. The volume of lung receiving greater than 20 Gy (V20) and mean lung dose are shown (37% and 20.2 Gy, respectively). The dose to 50% of the heart (D50) is shown (13.3 Gy), which is not a commonly used dose-volume metric but presented for illustrative purposes. The maximal dose to the spinal canal is depicted as well (49.5 Gy).

might be most weighted more heavily in the "summing," although this is less strongly considered in a parallel-structured organ. Early work in this area led to the Lyman, Kutcher Burman (LKB) model, and more recently the equivalent uniform dose (EUD) model, that both reduce a DVH to a single normal tissue complication probability (NTCP). These models and their relationships are summarized elsewhere.[1]

The Opportunities and Challenges of Modern Radiation Technologies

Several new radiation planning and delivery tools, such as intensity modulated radiation therapy (IMRT), image-guided radiotherapy (IGRT), stereotactic body radiotherapy (SBRT), and charged particle irradiation give the physician increased flexibility in determining how to deliver the desired target dose while minimizing or redistributing the dose exposure to normal tissue. The clinical application of these new technologies requires that the physician and dosimetrists/physicists have an in depth knowledge of the dose/volume/outcome relationships for critical normal tissues, hence the need for this chapter in this book. However, these new technologies have altered the relationship between the target doses and the doses to surrounding normal tissues that might impact the applicability of historic data for our modern era. With conventional beams (often opposed beam pairs treated sequentially), the normal tissues were exposed to fraction sizes similar to that of the tumor. With these newer approaches, the fractional radiation doses delivered to the normal tissues adjacent to the target are typically lower than that received by the target. Further, there is a movement toward the use of shorter hypofractionated regiments. Ironically, the use of increasing fractions sizes, along with an increasing number of beams, leaves (at least some of) the surrounding normal tissue receiving a daily fraction size close to what is typically seen with conventional approaches. However, with the more modern techniques, the heterogeneity of dose within the normal tissues is increased. Despite these caveats, much of the published data regarding radiation-associated normal tissue injury remains applicable in the modern era. Continued study of this important topic is clearly needed.

Broadly Defining Organ Structure

Normal tissues can be functionally defined as "serial," "parallel," or a combination of both, analogous to the terminology used for electrical circuits (Figure 14-2). In parallel functioning organs, the functional subunits function independently (i.e., functional redundancy exists). Thus, when some functional subunits of a parallel organ are damaged, the surrounding functional subunits continue to function. Examples of parallel functioning organs include lung, liver, and kidney. Small to moderate, and perhaps even large, volumes of parallel organs can be damaged without causing global dysfunction because there is enough reserve in the undamaged portion of the organ or there is a capacity to regenerate (e.g., liver). In "serial" organs, the functional subunits are arranged in a linear or branching fashion, and hence there is interdependence. Damage to the subunits of a serial organ can result in compromise or incapacity of the entire organ. Examples of series organs include spinal cord, portions of the central nervous system, peripheral and cranial nerves, gastrointestinal tract, and tracheal-bronchial tree. Although the concept of serial and parallel functioning organs is useful in assessing risk to tissues,

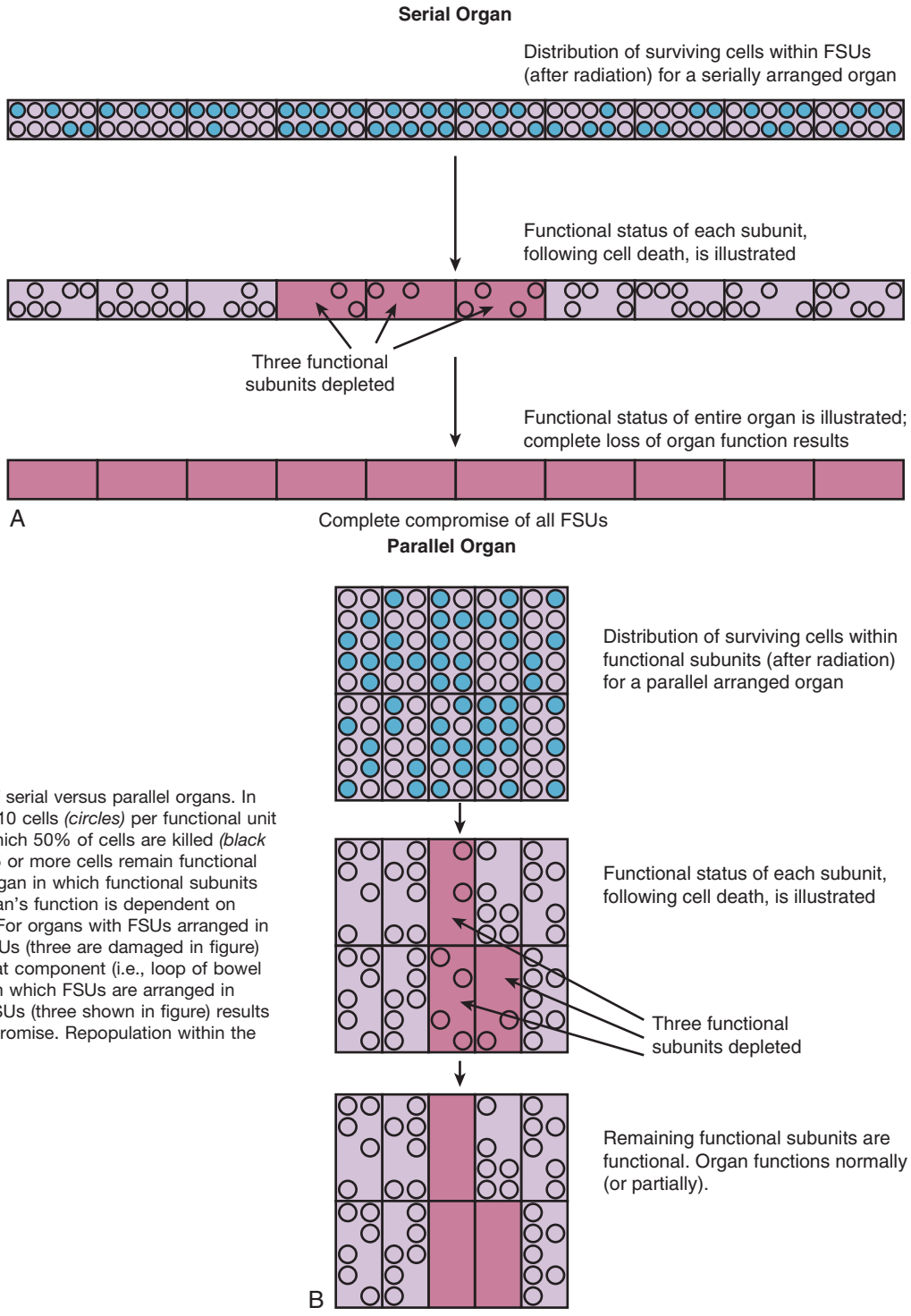

Figure 14-2 Illustrative comparison of serial versus parallel organs. In this figure, a hypothetical example of 10 cells *(circles)* per functional unit *(square)* is shown, after radiation in which 50% of cells are killed *(black circles)*, and functional subunits with 5 or more cells remain functional after radiation. Figure 1A shows an organ in which functional subunits (FSUs) are arranged in series; the organ's function is dependent on connectivity to its neighboring FSUs. For organs with FSUs arranged in series **(A),** damage to one or more FSUs (three are damaged in figure) results in complete compromise of that component (i.e., loop of bowel or region of spinal cord). For organs in which FSUs are arranged in parallel **(B),** damage to a portion of FSUs (three shown in figure) results in partial, or no apparent, organ compromise. Repopulation within the FSUs is not shown.

it should be appreciated that this is only a model. The function of many organs requires the integrity of both serial and parallel components (e.g., the lung requires the "parallel" alveoli, as well as the "series" conducting airways).

Further complicating this issue is the fact that, in both serial and parallel organs, there are often regional heterogeneities in function (e.g., gray matter and white matter tracts of the "parallel" spinal cord). These anatomic subregions may have different functions and different susceptibilities to treatment-related damage.

QUANTEC

This chapter will summarize and expand on several reviews published as a special issue in *International Journal of Radiation Oncology Biology Physics* (volume 76, issue 3, Supplement), all of which were written as part of the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) initiative. Because the QUANTEC reviews were published in 2010, this chapter also summarizes some studies published after QUANTEC.

QUANTEC arose from a proposal from the Science Council of the American Association of Physicists in Medicine (AAPM) to revise and update guidelines published by Emani in 1991.[2] QUANTEC's goals are (1) to provide a critical review of the current literature on quantitative dose-response and dose-volume relationships for clinically relevant normal-tissue endpoints; (2) to produce practical guidelines to allow reasonable toxicity risks based on dose-volume parameters; (3) to identify future research initiatives. Using the QUANTEC reviews as a backbone, this chapter will focus on recently published data relevant to late toxicity from radiation, with an emphasis on relevant dose-volume metrics. Key summary points of the QUANTEC reviews are briefly summarized at the end of each section, and the QUANTEC reviews are referenced after each subheading. Table 14-1 summarizes the dose-volume metrics that are supported by the literature; this table has been modified from the one published in the QUANTEC issue.[1]

Although the QUANTEC initiative and associated reviews addressed a broad range of issues relating to normal tissue damage, this chapter will focus on late toxicity after an initial course (i.e., excluding reirradiation) of conventional radiation (i.e., excluding hypofractionated regimens). Many of the individual QUANTEC reviews discussed brachytherapy, reirradiation, or hypofractionated radiation, particularly in the context of hypofractionated stereotactic body radiation and stereotactic radiosurgery. Future AAPM initiatives will focus on hypofractionated stereotactic radiation, a topic that is also reviewed elsewhere.[3,4] A separate initiative is under way addressing quantitative dose-volume relationships for pediatric survivors of cancer. This chapter will primarily focus on studies relating three dimensional dose-volume metrics to clinical outcomes.

NERVOUS SYSTEM: BRAIN

Organ Function and Clinical Significance

The structural and functional complexity of the brain puts this organ at risk for a spectrum of radiation-associated toxicities. Some specific functions of the brain can be correlated with

TABLE 14-1 Dose-Volume Metrics Supported by Published Data

Organ	Volume Segmented: Irradiation Type	Endpoint	Dose-Volume Parameters	Rate	Comments
Brain	Whole organ: 3DRT	Symptomatic necrosis	Dmax <60 Gy	<3%	Data at 72 and 90 Gy, extrapolated from BED models
	Whole organ: 3DRT	Symptomatic necrosis	Dmax <72 Gy	5%	
	Whole organ: 3DRT	Symptomatic necrosis	Dmax <90 Gy	10%	
Brainstem	Whole organ: whole brainstem	Permanent cranial neuropathy or necrosis	Dmax <54 Gy	<5%	
	Whole organ: 3DRT	Permanent cranial neuropathy or necrosis	D1-10 mL ≤59 Gy	<5%	
	Whole organ: 3DRT	Permanent cranial neuropathy or necrosis	Dmax <64 Gy	<5%	Point dose <1 mL
Optic nerve/ chiasm	Whole organ: 3DRT	Optic neuropathy	Dmax <55 Gy	<3%	Given the small size, 3DRT is often whole organ
	Whole organ: 3DRT	Optic neuropathy	Dmax 55-60 Gy	3%-7%	
	Whole organ: 3DRT	Optic neuropathy	Dmax >60 Gy	7%-20%	
Spinal cord	Partial organ: 3DRT	Myelopathy	Dmax 50 Gy	0.2%	Including full cord cross-section
	Partial organ: 3DRT	Myelopathy	Dmax 60 Gy	6%	
	Partial organ: 3DRT	Myelopathy	Dmax 69 Gy	50%	
Cochlea	Whole organ: 3DRT	Sensory neural hearing loss	Mean dose ≤45 Gy	<30%	Mean dose to cochlea, hearing at 4 kHz
Parotid	Bilateral whole parotids: 3DRT	Long-term parotid salivary function reduced to <25% of pre-RT level	Mean dose <25 Gy	<20%	For combined parotid glands
	Unilateral whole parotid: 3DRT	Long-term parotid salivary function reduced to <25% of preradiation level	Mean dose <20 Gy	<20%	At least one parotid gland spared to <20 Gy
	Bilateral whole parotids: 3DRT	Long term parotid salivary function reduced to <25% of preradiation level	Mean dose <39 Gy	<50%	For combined parotid glands
Pharynx	Pharyngeal constrictors: 3DRT	Symptomatic dysphagia and aspiration	Mean dose <50 Gy	<20%	
Larynx	Whole organ: 3DRT	Vocal dysfunction	Dmax <66 Gy	<20%	With chemotherapy
	Whole organ: 3DRT	Aspiration	Mean dose <50 Gy	<30%	With chemotherapy
	Whole organ: 3DRT	Edema	Mean dose <44 Gy V50 <27%	<20%	Without chemotherapy
Lung	Whole organ: 3DRT	Symptomatic pneumonitis	Mean dose 7 Gy	5%	Excludes purposeful whole lung irradiation
	Whole organ: 3DRT	Symptomatic pneumonitis	Mean dose 13 Gy	10%	
	Whole organ: 3DRT	Symptomatic pneumonitis	Mean dose 20 Gy	20%	
	Whole organ: 3DRT	Symptomatic pneumonitis	Mean dose 24 Gy	30%	
	Whole organ: 3DRT	Symptomatic pneumonitis	Mean dose 27 Gy	40%	

TABLE 14-1 Dose-Volume Metrics Supported by Published Data—cont'd

Organ	Volume Segmented: Irradiation Type	Endpoint	Dose-Volume Parameters	Rate	Comments
Esophagus	Whole organ: 3DRT	Grade ≥3 acute esophagitis	Mean dose <34 Gy		A variety of alternate threshold doses have been implicated
	Whole organ: 3DRT	Grade ≥2 acute esophagitis	V35 <50%		
	Whole organ: 3DRT	Grade ≥2 acute esophagitis	V50 <40%		Appears to be a dose/volume response
	Whole organ: 3DRT	Grade ≥2 acute esophagitis	V70 <20%		Similar constraints are applicable to late toxicity
Heart	Pericardium: 3DRT	Pericarditis	Mean dose <26 Gy		
	Pericardium: 3DRT	Pericarditis	V30 <46%		
	Whole organ: 3DRT	Long-term cardiac mortality	V35 <10%		Overly safe risk estimate based on model predictions
Liver	Whole liver—GTV: Whole liver or 3DRT	Classic RILD	Mean dose <30-32 Gy	<5%	Excluding patients with preexisting liver disease or hepatocellular carcinoma
	Whole liver—GTV: 3DRT	Classic RILD	Mean dose <42 Gy	<50%	
	Whole liver—GTV: Whole liver or 3DRT	Classic RILD	Mean dose <28 Gy	<5%	In patients with Child-Pugh a preexisting liver disease or hepatocellular carcinoma, excluding hepatitis B reactivation
	Whole liver—GTV: 3DRT	Classic RILD	Mean dose <36 Gy	<50%	
Kidney	Bilateral kidneys (not TBI) Bilateral kidneys or 3DRT	Clinically relevant renal dysfunction	Mean dose <15-18 Gy	<5%	
	Bilateral kidneys (not TBI) Bilateral kidneys	Clinically relevant renal dysfunction	Mean dose <15-18 Gy	<50%	
	Bilateral kidneys (not TBI) 3DRT (combined kidney)	Clinically relevant renal dysfunction	V12 <55% V20 <32% V23 <30% V28 <20%	<5%	
Stomach	Whole organ: Whole stomach	Ulceration	D100 <45 Gy	<7%	
Small bowel	Individual small bowel loops: 3DRT	Grade ≥3 toxicity (acute)	V15 <120 mL	<10%	Dose-volume data on late toxicity is lacking; data for acute toxicity data may be a reasonably good surrogate
	Peritoneal cavity: 3DRT	Grade ≥3 toxicity (acute)	V45 <195 mL	<10%	
Rectum	Whole organ: 3DRT	Grade ≥2 toxicity Grade ≥3 toxicity	V50 <50%	<15% <10%	Data derived mostly from prostate cancer treatment
	Whole organ: 3DRT	Grade ≥2 toxicity Grade ≥3 toxicity	V60 <35%	<15% <10%	
	Whole organ: 3DRT	Grade ≥2 toxicity Grade ≥3 toxicity	V65 <25%	<15% <10%	
	Whole organ: 3DRT	Grade ≥2 toxicity Grade ≥3 toxicity	V70 <20%	<15% <10%	
	Whole organ: 3DRT	Grade ≥2 toxicity Grade ≥3 toxicity	V75 <15%	<15% <10%	
Bladder	Whole organ: 3DRT	RTOG grade ≥3 late toxicity	Dmax <65 Gy	<6%	Based on bladder cancer treatment
	Whole organ: 3DRT	RTOG grade ≥3 late toxicity	V65 <50% V70 <35% V75 <25% V80 <15%	<6%	Variations in bladder size, shape, location during radiation hamper ability to generate accurate data
Penile bulb	Whole organ: 3DRT	Severe erectile dysfunction	Mean dose to 95% of gland <50 Gy	<35%	
	Whole organ: 3DRT	Severe erectile dysfunction	D90 <50 Gy	<35%	
	Whole organ: 3DRT	Severe erectile dysfunction	D60-D70 <70 Gy	<35%	

3DRT, *3-dimensional conformal radiotherapy;* BED, *biologically effective dose;* Dmax, *maximum radiation dose;* Dx, *minimum dose received by the "hottest" x% (or x cc) of the organ;* RILD, *radiation-induced liver disease;* TBI, *total body irradiation;* Vx, *volume of the organ receiving ≥ x Gy.*

All at standard fractionation (i.e., 1.8 Gy to 2.0 Gy per daily fraction). All data are estimated from the literature summarized in the QUANTEC reviews and in the chapter. 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.

discrete location(s) within the brain, whereas others are spread throughout the brain. Primary toxicity endpoints include frank brain necrosis with associated symptoms or signs and neurocognitive decline.

Dose-Volume Data

Prospective studies in adults have shown that partial (and limited) brain irradiation in the dose range of 50 Gy to 60 Gy, causes minimal to no discernible effect on memory and cognition.[5-10] However, another study has suggested that patients undergoing partial brain radiation for low-grade glioma, versus patients who do not undergo radiation, are at greater risk for neurocognitive deficits, particularly attention, executive functioning, and information processing.[11] More detailed studies, correlating neurocognition with susceptible regions within the brain, are needed. Certainly, ample data suggest that the volume of brain that is irradiated affects the degree of radiation-associated neurocognitive decline (with whole brain radiation faring worse).[12] In adult patients who have received whole brain radiation, neurocognitive decline is well described. However, the degree to which the brain radiation (versus other factors such as surgery, a history of hydrocephalus, other chronic diseases and comorbid illnesses, chemotherapy exposure, and tumor progression) impacts neurocognitive function is not clear.[10,13,14]

There has been growing interest in the hypothesis that minimizing radiation dose to the hippocampal or subventricular zone stem cell niches can reduce the risk of neurocognitive deficits.[15] However, it is not known if there are particular critical individual avoidance structures (or regions) or combination of avoidance structures, nor whether there are well-defined dose-volume thresholds and what these dose-volume limits might be. In a prospective study of 18 patients with low-grade glioma treated at the University of Wisconsin, a dose of >7.3 Gy (in 2 Gy equivalents) to the bilateral hippocampi was significantly associated with impairment in delayed recall, whereas any dose (i.e., dose in excess of 0 Gy) trended toward significance.[16] In the RTOG 0933 Phase II study of hippocampal sparing (100% dose and maximum dose to not exceed 10 Gy and 17 Gy, respectively) in 113 patients with brain metastases, memory preservation at 4 and 6 months (measured by the Hopkins Verbal Learning Test Delayed Recall) was significantly better than historical controls.[17] In a study of 75 patients with pituitary adenoma, 30 of whom had undergone 3-5 field pituitary irradiation to a dose of 45 Gy, neither hippocampal dose nor prefrontal cortex dose correlated with cognitive outcomes.[18]

A prospective study of pediatric patients correlated hippocampal, temporal, and cerebral doses with objective neurocognitive measures.[19] For children, younger age at radiation and larger irradiated volumes (with higher doses having a greater impact) are associated with objectively worse neurocognitive function.[20-23] For example, central nervous system prophylaxis for acute lymphoblastic leukemia with 24 Gy whole brain radiation in addition to intrathecal methotrexate (versus methotrexate alone) resulted in a median 13 point IQ reduction at 5 years postradiation and poorer academic achievement, self-image, and greater psychological distress at 15 years.[24] Lower risks are associated with lower doses of 14 Gy to 18 Gy.[25-27] For medulloblastoma, increasing brain dose in the 18- to 36-Gy range has been correlated with greater neurocognitive decline.[20-22,28,29] Girls were observed to be more vulnerable to injury than boys.[30] Reported toxicities were lower (or not detected) when 14 Gy to 18 Gy was used.[25-27] A recent study has shown that increased dose (from 0 Gy to 24 Gy) and younger age at diagnosis are correlated with worse neurocognitive outcomes that increased with time from diagnosis; furthermore, chemotherapy in the absence of radiotherapy (particularly methotrexate-based chemotherapy), resulted in severe impairment of complex neurocognitive processes, similar to impairment after cranial radiation dose in excess of 18 Gy.[31]

Radiation necrosis can occur in any part of the brain. Although there may be regional variations of susceptibility within the brain related to differences in vascularity, glial cell population, and so on, this data is sparse, and it is generally believed that location does not generally affect susceptibility to necrosis. However, certain regions, such as the brainstem, are more likely to cause symptoms. There is a paucity of data correlating dose-volume parameters with the risk of radiation necrosis with conventional fraction, though many studies have documented an association of fraction size with the risk of necrosis.

In a study from Queen Elizabeth Hospital in China, 1008 patients with nasopharyngeal cancer, treated prior to 1985, received 45.6 Gy to 53.2 Gy in 3.8 Gy fractions, 50.4 Gy in 4.2 Gy fractions or 60 Gy in 2.5 Gy fractions.[32] The 10-year risk of temporal lobe necrosis was 18.6% in those treated with 4.2 Gy fractions versus <5% for the other dose schemes ($p < 0.001$). A multiinstitutional Chinese study examined 1032 patients with nasopharyngeal cancer treated after 1990 with one of several fractionation schemes (mostly 2 Gy to 3.5 Gy fractions, though one scheme used a 1.6 Gy twice-daily component).[33] The 5-year actuarial incidence of necrosis ranged from 0% (after 66 Gy in 2 Gy fractions) to 14% (after 2.5 Gy × 8 followed by 1.6 Gy twice daily to 71.2 Gy). In both of the aforementioned studies, the product of total dose and dose per fraction significantly impacted risk; shorter overall treatment time and twice-daily fractionation also increased risk. A Chinese study comparing 71.2 Gy in 1.6 Gy twice-daily fractions versus 60 Gy in 2.5 Gy fractions was terminated early because of excessive neurologic toxicity, including temporal lobe toxicity, in both arms. The risk of toxicity was greater, and the interval to developing toxicity was shorter, with the twice-daily regimen.[34] In another Chinese study, 27% of patients receiving an accelerated hyperfractionated regimen (64 Gy in 1.6 twice-daily fractions) versus 0% receiving hyperfractionated radiation (70.8 Gy in 1.2 Gy twice-daily fractions) developed symptomatic radiation necrosis.[35]

Radiation necrosis has also been studied in patients with primary brain tumors. The risk is dose dependent, with doses of <50 Gy rarely causing necrosis.[36-38] In patients treated for brain metastases, there was a low (<2%) risk of necrosis developing after 1.6 Gy twice daily to the whole brain (32 Gy) followed by a boost to 54.4 to 74.4 Gy, and no necrosis was seen after a boost to 48 Gy.[39,40]

Summary and Other Key Points from QUANTEC Review[41]

A high level of evidence to quantify the risks of radiation-induced brain injury is lacking. For brain necrosis, the brain appears to be especially sensitive to fraction size in excess of 2 Gy, and to twice-daily fractionated treatment. Symptomatic necrosis is uncommon with doses <60 Gy with conventional (1.8 Gy to 2 Gy) fractionation, though the risk increases with increasing dose (see Table 14-1). More detailed studies correlating neurocognition with susceptible regions within the brain are needed. Long-term (>5 years) follow-up is necessary to best assess neurological and cognitive decline. For children, younger age and higher whole brain dose strongly correlate with cognitive decline. Future studies should provide a clear definition of toxicity and report actuarial (as opposed to crude) rates that can be correlated with detailed normal brain dose-volume metrics.

NERVOUS SYSTEM: BRAINSTEM

Organ Function and Clinical Significance

The brainstem serves as a conduit from the brain to the cranial nerves and spinal cord. As a result, the brainstem is involved with motor, sensory, and special sensory function, as well as regulation of temperature, cardiac function, respiratory function, and consciousness. It is well accepted that the entire brainstem may be treated to 54 Gy using conventional fractionation with minimal risk of late brainstem toxicity. Small volumes of brainstem may tolerate higher doses. Similar to the brain, the brainstem is heterogeneous, and it is not well known which regions are most susceptible to radiation-induced damage.

Dose-Volume Data

Several institutions have published their dose-volume constraints for brainstem, most of which have not reported any brainstem toxicity. These constraints for patients undergoing external beam radiation therapy for head and neck cancers include V60 <5 mL, V65 3 mL,[42] V55 <0.1 mL,[43] D1 <54 Gy,[44] and maximum <50 Gy[45]; for patients undergoing proton or combined proton/photon therapy for base of skull lesions the constraints include: <63 Gy to 64 Gy CGE to the brainstem surface and 53 to 54 CGE to the brainstem center.[46-49]

Some patients in these studies received a maximum brainstem dose of 66 CGE to 68 CGE (greater than the recommended constraints) to adequately treat the tumor.[46,48,49] In one study, the dose constraint of 63 CGE to the brainstem surface and 54 CGE to the brainstem center was "relaxed" in 38% and 17% of patients, respectively, with no reported neurologic toxicity. In these patients, the volume receiving more than the threshold dose was 0.2 mL and 1.2 mL for the brainstem surface and center, respectively.[48] In another study, two of four patients developing neurologic toxicity received brainstem maximal doses in excess of 64 Gy CGE to the surface and 53 CGE to the center.[49]

In an analysis of 367 patients from Massachusetts General Hospital, an increased risk of late toxicity was associated with the maximal delivered dose (>64 CGE), V50 (>5.9 mL), V55 (>2.7 mL), V60 (>0.9 mL), history of diabetes, hypertension, and more than two surgical procedures of the base of skull, on univariate analysis.[50,51] On multivariate analysis, only V60, history of diabetes and more than two surgical procedures remained significant. A V60 <0.9 mL compared to >0.9 mL resulted in toxicity-free survival of 96% compared to 79% (p = 0.0001), and on multivariate analysis resulted in an 11.4 risk ratio (p = 0.001). In a study from St. Jude Children's Research Hospital on 68 patients with infratentorial ependymoma, several interrelated variables were associated with brainstem injury, including tumor volume (and thus radiation volume), surgical morbidity, male gender, younger patient age, and cerebral spinal fluid shunting. The radiation dose was homogeneous between 54 Gy and 59.4 Gy.[52]

In a study of 40 patients undergoing IMRT for meningioma, one patient developed fatal brainstem necrosis after receiving a maximum dose to the brainstem of 55.6 Gy, with 4.74 mL exceeding 54 Gy.[53] This demonstrates that other poorly understood factors likely increase the risk of brainstem toxicity because this dose constraint would be considered acceptable in most of the studies referenced previously.

Summary and Other Key Points from QUANTEC Review[54]

Investigating radiation-induced brainstem injury is challenging because of the low incidence of toxicity with conventional doses, the short survival of patients, and the challenges of distinguishing between tumor progression and toxicity. Whole brainstem doses <54 Gy appear to be safe. Small volumes of brainstem appear to tolerate doses in excess of 55 Gy to 60 Gy. The risk of brainstem necrosis is low if the volume receiving >60 Gy is <0.9 mL.

NERVOUS SYSTEM: SPINAL CORD

Organ Function and Clinical Significance

The spinal cord consists of the motor and sensory tracts, communicating information between the peripheral nerves and the brain. Radiation-induced spinal cord injury can result in pain, paresthesias, sensory deficits, paralysis, Brown-Séquard syndrome, and bowel/bladder incontinence.

Dose-Volume Data

It is well accepted that the spinal cord can tolerate 45 Gy to 50 Gy with conventional fractionation, though the dose resulting in 5% toxicity risks (TD5) is most likely much higher. The spinal cord is generally limited to 45 Gy to 50 Gy because the anticipated risk of cord injury must be low to be clinically acceptable. In an analysis of several studies, Schultheiss calculated the probability of cervical cord myelopathy, after full cross-sectional irradiation, as 0.03% after 45 Gy, 0.2% after 50 Gy, and 5% after 59.3 Gy.[55] The thoracic spinal cord was calculated to be less sensitive than the cervical spinal cord (though because of the dispersion of data, a good fit could not be obtained). This model does not incorporate spinal cord volume, which might be acceptable given the "series" nature of the cord. Nevertheless, Schultheiss cautions that long lengths of cord, concomitant chemotherapy, and other factors may increase risk.

Little data exists exploring the dose-volume tolerance of the spinal cord. No spinal cord toxicity was reported in a study in which the V50 was <0.1 mL,[43] or in another study in which the D1 <45 Gy.[44] Massachusetts General Hospital studied 85 patients treated to the cervical spinal cord in the range of 45 Gy to 59.4 Gy (1.5 Gy equivalent fractions) equivalent uniform dose (EUD), 42 Gy to 57.5 Gy maximal dose to cord center, and 57 Gy to 74 Gy maximal dose to cord surface.[56] Fifteen percent of these patients experienced L'hermitte syndrome (self-limited symptoms of electric shocklike sensation most notable with neck flexion, attributable to focal demyelination) and 5% developed objective neurologic findings at or below cord level treated. Toxicity was not significantly correlated with cord length, cord volume, maximal dose to cord center, maximal dose to cord surface or effective uniform dose. The authors conclude that an EUD to the cervical cord of 60 Gy in 1.5 Gy fractions or 52.5 Gy in 2 Gy fractions is safe. In a recent study of 437 patients with laryngeal or oropharyngeal carcinoma (with maximum spinal cord dose of 22 Gy to 69 Gy) none developed myelopathy (at a median follow-up 27 months) whereas 17 developed L'hermitte's sign; the average spinal cord V45 of these 17 patients was 14 mL compared to 8 mL for those without L'hermitte's sign.[57] It has been postulated that the dose to the spinothalamic tract is most clinically significant for the occurrence of L'hermitte's sign.[58]

Summary and Other Key Points from QUANTEC Review[59]

There is not yet a consensus on the best approach to delineating the spinal cord, with options including delineating the entire thecal sac, the spinal canal, the spinal cord (as seen on magnetic resonance imaging [MRI]) or the spinal cord plus a

several millimeter margin. Though rare, radiation-induced spinal cord injury can be clinically devastating. With conventional fractionation of 1.8 Gy to 2.0 Gy per fraction to the full thickness of the spinal cord, the estimated risk of spinal cord myelopathy is <1%, <10%, and 50% at 54 Gy, 61 Gy, and 69 Gy, respectively. Although there is limited data on high dose per fraction using conventional radiation techniques, the estimated α/β ratio of 0.87 suggests a strong dependence of spinal cord toxicity on dose/fraction. Small volumes of spinal cord can likely receive doses in excess of 55 Gy to 60 Gy (with the high doses limited to the surface) with low risk of toxicity, though long-term data are lacking to derive a dose/volume relationship for myelopathy risk. Thus, recommendations for safe dose-volume metrics above 55 Gy to 60 Gy are lacking.

NERVOUS SYSTEM: OPTIC NERVES AND CHIASM

Organ Function and Clinical Significance

The optic nerve and chiasm serve as the neural conduit connecting the retinal fibers to the optic tracts, which, via the lateral geniculate body, terminate in the visual cortex. It is generally accepted that the entire optic nerves and chiasm may be treated to 54 Gy using conventional fractionation with minimal risk of late visual toxicity, though lower doses can result in other ophthalmologic toxicity.[60] A classic study showed that among patients treated to the same dose for pituitary adenomas or craniopharyngiomas, those who developed optic neuropathy (5 to 34 months after radiation) had received ≥2.5 Gy per fraction.[61] In a study from M. D. Anderson Cancer Center (MDACC), in which 219 patients were treated in the pre-3D radiation era, 10-year actuarial rates of optic neuropathy were 0%, 3%, and 34% for 43 Gy to 49 Gy at ~1.9 Gy/fraction, 50 Gy to 60 Gy at ~2.1 Gy/fraction, and 61 Gy to 76 Gy at ~2.2 Gy/fraction, respectively. Chiasm damage was similar with rates of 0%, 8%, and 24% for 15 Gy to 49 Gy at ~1.5 Gy/fraction, 50 Gy to 60 Gy at ~2.0 Gy/fraction, and 61 Gy to 76 Gy at ~2.1 Gy/fraction, respectively.[62] Greater total dose as well as larger fraction size impact risk.[63-66] With 3D planning, small volumes of optic nerve and chiasm may tolerate higher doses.

Dose-Volume Data

Several institutions have published their dose-volume constraints for the optic nerves and chiasm, most of which have not reported any neurologic visual toxicity. These constraints for patients undergoing external beam radiation therapy for head and neck cancers include V55 <0.1 mL of optic nerves/chiasm,[43] D1 <54 Gy for optic nerves, and D1 <45 Gy for optic chiasm[44] and maximum <54 Gy to the optic nerves and 52 Gy for the chiasm. These dose constraints are more conservative compared to what has been reported with proton therapy for base-of-skull tumors; base-of-skull tumors may be in close proximity to the optic apparatus, and tumors such as chordomas and chondrosarcomas are prescribed relatively high doses. For patients undergoing proton or combined proton/photon therapy for base-of-skull lesions, published dose constraints include <55 CGE to 56 GGE[47-49] or <60 Gy CGE[46] to optic nerves and optic chiasm.

Several studied have reported ophthalmologic toxicity after radiation. In a study from the University of Florida, the optic nerve dose (defined as the minimum dose delivered to one third of the optic nerve) in patients who developed optic neuropathy was 50.4 Gy to 79 Gy (median 68 Gy).[66] In a University of Michigan study, seven patients developed ophthalmologic toxicity: one patient received a chiasm maximum of 59.5 Gy; six patients received an optic nerve maximum of 47.5 Gy to 75.5 Gy (average 63 Gy).[67] Moderate to severe optic nerve complications (four patients) were associated with doses >64 Gy. In one study, four patients developed ophthalmologic toxicity, of whom three received a maximal dose of 56 CGE to 62 CGE to the optic chiasm/nerves and one received a maximum dose of >62 CGE. In two studies, bilateral visual loss occurred, with no evidence of tumor progression, ~8 months after conventional radiation; in one, the prescribed target dose was 49.3 Gy (maximum dose 56.1 Gy; chiasm maximum not reported, but <1 mL received >45 Gy)[68]; and in the other the chiasm maximum was <58 CGE.[47]

Some patients appear to tolerate a maximum optic nerve or chiasm dose of >60 Gy or >63 CGE to 69 CGE.[45,46,48,49,67] This demonstrates that other poorly understood factors likely increase the risk of optic nerve and chiasm toxicity. Optic nerve maxima >80 Gy and chiasm maxima >70 Gy were tolerated in some patients in the University of Michigan study discussed previously.[67] In another study, the dose constraint of 56 CGE to the optic nerve and chiasm was "relaxed" in 28% and 48% of patients, respectively, with no reported visual toxicity. In these patients, the volume receiving above the threshold dose was 0.11 mL and 0.12 mL for the optic nerves and chiasm, respectively; the volume receiving >105% of the threshold dose was 0.05 mL and 0.01 mL.[48]

Summary and Other Key Points from QUANTEC Review[69]

Data clearly show that the total dose and fraction size are the most important treatment-related risk factors for optic nerve/chiasm injury. There are scarce data to suggest a dose-volume effect on the optic nerve and chiasm. The risk of visual problems is <3% with <55 Gy, 3% to 7% for 55 Gy to 60 Gy, and >7% for >60 Gy. In the 55 Gy to 60 Gy experience, almost all of the reported cases of optic nerve injury received doses in the 59- to 60-Gy range (i.e., the high edge of that dose range).

NERVOUS SYSTEM: HEARING

Organ Function and Clinical Significance

The cochlea and acoustic nerve are the essential auditory structures that are susceptible to radiation injury and consequential sensory neural hearing loss. These are small structures, and therefore dose-volume measures are less determinable and clinically relevant. Other dose-dependent susceptible parts of the auditory system include the external ear and ear canal, tympanic membrane, ossicles, and eustachian tube.[70] Platinum based chemotherapy also is a well-established cause of sensory-neural hearing loss. Other factors such as baseline function and patient age are also relevant.

Dose-Volume Data

Several studies suggest that the dose to the cochlea correlates with the rate of sensory-neural hearing loss. A study from University of Florida showed that incidence of sensory-neural hearing loss increased consistently with dose to the cochlea; the 10-year actuarial risk of sensory neural hearing loss was 3% at doses <60.5 Gy compared to 37% at doses >60.5 Gy.[70]

Several other studies have shown hearing loss to be directly related to the inner-ear dose,[71-76] with sensory neural hearing loss becoming more apparent at doses >45 Gy to 50 Gy.[72,74,75,77] A German study examined hearing loss during and after radiotherapy for patients with head and neck cancers; for bone and air conduction after radiation, a 15-dB reduction in 50% of

patients over a range of frequencies was in the 20-Gy to 30-Gy range of doses to the inner ear (which ranged from 1.7 Gy to 64.3 Gy).[76] Cisplatin dose is also relevant to the threshold for auditory impairment. Cisplatin doses as low as 270 mg/m^2 can result in hearing loss when combined with cranial radiotherapy dosages of 40 Gy to 50 Gy.[78] In one study of patients with head and neck cancers, in those treated with radiation alone, hearing loss developed with cochlear doses >40 Gy; however, among those who received cisplatin (100 or 40 mg/m^2) and radiation, hearing loss developed with cochlear doses >10 Gy,[79] although the risk is likely low below doses of 30 Gy. The sequence of chemoradiotherapy also appears to influence risk. Risk and severity of ototoxicity are greater when cisplatin is administered after cranial radiation.

In a recent study of patients with base-of-skull tumors treated with radiation (median 50.4 Gy) radiographic opacification of the middle ear or mastoid, which correlates with subacute/chronic otitis media with effusion, occurred in 40 of 61 patients (with median follow-up of 21 months); this resolved in 17 of 40 patients 2 to 45 months (mean 17) after radiation.[80] Dose-volume analyses were performed for the eustachian canal, middle ear, mastoid air cells, vestibular apparatus, cochlea, internal auditory canal, lateral and posterior nasopharynx, and temporal lobes. Multivariate analysis showed that mastoid dose >30 Gy (odds ratio = 28.0, $p < 0.001$) and posterior nasopharynx dose >30 Gy (odds ratio = 4.9, $p = 0.009$) were associated with Grades 2 to 3 middle ear effusions.

Summary and Other Key Points from QUANTEC Review[81]

Because of the small volume of the cochlea, quantifying mean dose to the cochlea is more feasible than a dose/volume measure. Based on available data, the cochlear mean dose should be limited to ≤45 Gy (or more conservatively ≤30 Gy) and should be more strictly limited when delivered with cisplatin chemotherapy.

SALIVARY GLANDS

Organ Function and Clinical Significance

The salivary glands produce saliva, which aids in the swallowing, lubricating the oral cavity, taste, and food digestion. The parotid glands generate ~60% of saliva, and the majority of serous saliva, with the remainder of saliva secreted by submandibular, sublingual, and minor salivary glands. Radiation-induced salivary gland dysfunction—xerostomia—can result in difficulty swallowing, altered taste, and an increased risk of dental caries and oral infections. Because of the proximity of the parotid glands to the Level II lymphatics, IMRT is often used in the treatment of patients with head and neck cancers to reduce the parotid dose, in an attempt to prevent xerostomia.

Dose-Volume Data

The University of Michigan has published several studies investigating radiation dose-volume effects on serially measured stimulated and unstimulated salivary flow (directly from a given parotid gland). With salivary flow measured up to 12 months after radiation, significant parotid sparing was observed after a mean parotid dose below 24 Gy (for unstimulated flow) to 26 Gy (for stimulated flow).[82-84] Mean doses correlated with V15 of ≤67%, V30 of ≤45%, and V45 of ≤24%. The TD50 was 28.4 Gy.

Investigators at Washington University also examined whole salivary flow. Their technique differed from that from the University of Michigan in that they measured flow from all glands, though they included only patients whose submandibular glands received >50 Gy in an attempt to minimize this confounding variable.[85,86] Salivary flow was noted to be exponentially reduced by ~0.054/Gy of mean parotid dose (i.e., $e^{(-0.054^* \text{ mean dose})}$), equating to a reduction to 25% of the pr-treatment salivary flow with a mean dose of 25.8 Gy, essentially equivalent to the University of Michigan number.[87] The mean dose model was more predictive of the risk of late effects than threshold dose levels of V5 to V70 as well as other models studied.

Other groups have corroborated the mean dose as significant variable impacting salivary function,[88-93] with a Belgian study suggesting a lower threshold mean dose of 22.5 Gy.[94] A Dutch group demonstrated the TD50 for stimulated salivary function (risk of <25% of pretreatment rates) to improve with time, with TD50s of 34 Gy at 6 weeks to 40 Gy at 6 months, 42 Gy at 12 months, and 46 Gy at 5 years.[95,96] In a University of Michigan study, with flow rates measured in 142 patients up to 24 months after radiation, salivary flow rate was modeled as a function of time.[97] With mean parotid doses <25 Gy, the model predicted salivary function recovery to pretreatment functioning at 12 months. For mean parotid doses >30 Gy, stimulated saliva did not return to pretreatment functioning after 2 years.

In the parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT) trial, 94 patients with T1-4N0-3M0 pharyngeal squamous cell carcinoma were randomized (of whom 73 were evaluable for xerostomia).[98] IMRT compared to conventional radiotherapy allowed significant lowering of the ipsilateral (mean 25.4 Gy versus 61.0 Gy) and contralateral (mean, 47.6 Gy versus 61.0 Gy) parotid dose and resulted in a significantly lower incidence of xerostomia and greater recovery of salivary function 1 and 2 years after therapy. Randomized studies of IMRT in patients with nasopharyngeal cancer have shown similar findings.[99,100] In a recent study of 126 patients from Germany, restraining the mean dose to both parotids <26 Gy (versus only one) significantly reduced xerostomia and dysphagia.[101]

Radiation dose to the submandibular glands also impacts salivary function.[102] In a study from Helsinki University, the mean unstimulated salivary flow was 60% of the pretreatment function among patients who had one submandibular gland spared (mean dose of 26 Gy and range from 21 to 34 Gy) and 25% among those who did not ($p = 0.006$).[103] However, sparing of a submandibular gland did not affect the *stimulated* saliva flow rates. Another study showed that intentional sparing of submandibular glands (average mean dose of 20.4 Gy and V30 of 14.7%) versus no submandibular gland sparing (average mean dose 57.4 Gy and V30 99.8%), resulted in a nonsignificant trend toward better recovery of salivary flow.[104] Investigators at Vrije University in Amsterdam have demonstrated that mean submandibular dose is a significant variable impacting the sensation of sticky saliva.[105] In addition to submandibular dose and parotid gland dose, the University of Michigan group showed that oral cavity dose (containing the minor salivary glands) is also predictive; although no well-defined thresholds were observed, an oral cavity mean dose of <40 Gy was associated with low xerostomia rates.[106] The Radiation Therapy Oncology Group (RTOG) has demonstrated the feasibility and efficacy of surgically transferring the submandibular salivary gland to the submental space and shielding (>70%) of this gland during radiation to mitigate xerostomia.[107]

NTCP modeling of 178 patients treated with IMRT showed that baseline salivary function and mean contralateral parotid gland dose were predictors for xerostomia, and that mean contralateral submandibular gland dose, mean sublingual dose, and mean dose to minor salivary glands in the soft palate were predictive for sticky saliva.[108,109]

Summary and Other Key Points from QUANTEC Review[110]

Several studies have nicely demonstrated a dose response relationship between the salivary flow and mean parotid dose. From the available data, it appears that severe long-term salivary dysfunction (generally defined as reduction of salivary flow to less than 25% of baseline) can be avoided if one parotid gland is spared to a dose of less than 20 Gy or if both parotid glands have a mean dose of less than 25 Gy. A recent clinical study confirmed that adherence to these guidelines effectively avoids xerostomia.[111] Much of the data on submandibular gland and minor salivary gland dose-volume effects discussed previously were published in recent years, after QUANTEC was published.

LARYNX AND PHARYNX

Organ Function and Clinical Significance

The larynx and pharynx are involved with phonation and swallowing, respectively. Late complications include laryngeal edema and fibrosis, laryngeal dysfunction, dysphagia, and necrosis. A study from University of Michigan showed that damage to the pharyngeal constrictors and the glottic and supraglottic larynx may cause dysphagia and aspiration after chemoradiation.[112]

Dose-Volume Data: Larynx

For laryngeal edema, in a study from University of Texas, Galveston (with most patients receiving radiation alone), the mean laryngeal dose and laryngeal V30 to V70 were significantly associated with grade ≥2 edema with a univariate analysis, whereas mean laryngeal dose and N stage were significant with multivariate analysis.[113] V50, which was highly correlated with mean laryngeal dose, was significant in a multivariate analysis in which mean laryngeal dose was replaced by V50. The 1-year rate of grade ≥2 edema was 20% after a mean laryngeal dose of 43.5 Gy (or V50 <27%) versus 45% after a mean dose of 44 Gy to 57 Gy (or 94%< V50 >27%) versus >80% after a mean dose >57 Gy (or V50 >94%).

There is a paucity of data correlating dose-volume metrics with vocal dysfunction. Generally, after therapeutic doses of 60 Gy to 66 Gy for early stage glottic cancer, the risks of vocal dysfunction are low. In a study from University of Iowa, point doses in excess of 66 Gy to the aryepiglottic folds, preepiglottic space, false vocal cords, and lateral pharyngeal walls resulted in a sharp increase in risk of vocal function.[114]

Summary and Other Key Points from QUANTEC Review[115]

Radiation-induced laryngeal edema is a common and expected side effect. Progressive edema and associated fibrosis[116] can lead to long-term problems with phonation as well as swallowing. Tumor infiltration, particularly with locally advanced cancers can cause voice and swallowing symptoms, and may exacerbate radiation toxicities. To minimize risks of laryngeal edema, a larynx V50 ≥27% and the mean laryngeal dose of ≤44 Gy are recommended.

Dose-Volume Data: Swallowing

Several studies have investigated dose-volume metrics predictive of swallowing dysfunction, with many studies published after the QUANTEC report. In a study from University of Michigan, mean dose to the pharyngeal constrictors was correlated to risk of aspiration.[117] The risk of aspiration increased with a mean dose of >60 Gy to the pharyngeal constrictors, and with a V40 >90%, V50 >80%, V60 >70%, and V65 >50%, and with a V50 >50% for the larynx. Three patients who developed strictures had a pharyngeal constrictor V70 >50%.

In a study from Aarhus University, several significant correlations were found between both subjective and objective swallowing problems and DVH parameters of the base of tongue, pharyngeal constrictors, supraglottic larynx, esophageal sphincter, and glottic larynx.[118] Doses less than 60 Gy to the supraglottic region, the larynx, and upper esophageal sphincter resulted in a low risk of swallowing difficulties and aspiration.

In a study from University of Iowa, point doses to the false vocal cords, lateral pharyngeal walls, and the upper esophageal sphincter were correlated with dietary difficulties.[114] As an example, the dose to the left lower pharyngeal wall for patients who had no oral intake 1 year after treatment was 79.7 Gy versus 65.1 Gy for those with an unrestricted diet. A greater radiation dose to the aryepiglottic folds was associated with greater weight loss and a great radiation dose to the false vocal cords was associated with gastrostomy tube use.

In a study from Rotterdam, doses >50 Gy to the middle and superior pharyngeal constrictors resulted in a 20% probability of dysphagia, with an incremental 19% risk for each additional 10 Gy.[119] Another study (of 39 patients) suggested that the dose (V60 to V65 and mean) to the inferior pharyngeal constrictors is most predictive of gastrostomy tube dependence,[120] whereas in two other studies (of 50 and 53 patients),[121,122] the V50 (one study) and mean dose (both studies) of the middle pharyngeal constrictors were most predictive of dysphagia, along with mean supraglottic larynx dose (one study).[122] In an analysis of 96 patients from the Dana-Farber Cancer Institute, the inferior pharyngeal constrictor V50 and larynx V50 were significantly associated with aspiration and stricture risk.[123] MDACC investigators recommended a V30 <65% and V35 <35% for anterior oral cavity and V55 <80% and V65 <30% for superior pharyngeal constrictors, which was predictive for swallowing dysfunction in 31 patients.[124] University of Alabama at Birmingham investigators recommended V60 <24% to the larynx and <12% to the inferior pharyngeal constrictors to reduce risk of aspiration and gastrostomy tube dependence, and V65 <75% to the middle pharyngeal constrictors, and <33% to the superior pharyngeal constrictor to reduce risk of stricture requiring dilation.[125] In a Nordic study of 354 patients,[126] mean dose to the superior pharyngeal constrictor and supraglottic larynx were most predictive of radiation-induced swallowing dysfunction; different models (resulting in different significant dosimetric variables) were developed specifically for dysphagia to liquids, soft foods, or solids.

A recent analysis, based upon 53 of 189 patients who developed grade ≥3 dysphagia, designed a predictive model by analyzing clinicopathologic, treatment, and dosimetric parameters (dose to pharyngeal constrictor and esophageal structures) as well as genetic polymorphisms; the best model incorporated concurrent chemotherapy, dose to 2% of the pharyngeal constrictors and an XRCC1 polymorphism.[127]

Summary and Other Key Points from QUANTEC Review[115]

Because swallowing is complex, involving voluntary and involuntary stages coordinated through several cranial nerves and muscles, defining the most important anatomic structures whose dose-volume parameters have a major impact on dysphagia has been challenging. Emerging data has demonstrated

significant correlations between pharyngeal constrictor doses and dysphagia. With limited available data, it is recommended to limit the volume (to the extent possible without compromising target coverage) of the pharyngeal constrictors and larynx receiving ≥60 Gy, and reducing when possible the volume receiving ≥50 Gy. From data published after the QUANTEC review, it is readily apparent that mean dose and dose in excess of 50 Gy to 60 Gy to the larynx and pharyngeal constrictor muscles are predictive of swallowing difficulties, though it is unclear which of the pharyngeal constrictor muscles and which component(s) of the larynx are most critical.

LUNG

Organ Function and Clinical Significance

The lung's main function is gas exchange of oxygen and carbon dioxide. Radiation damage to the lung can result in symptomatic pneumonitis and fibrosis. Symptomatic radiation pneumonitis is characterized by dyspnea, cough, and sometimes a low-grade fever, typically occurring several weeks to months after radiation. More long-term lung fibrosis can lead to respiratory insufficiency. It is often challenging to distinguish radiation-related pulmonary symptoms from comorbid illnesses (e.g., exacerbation of chronic obstructive pulmonary disease, infection, cardiac events).[128] Objective reductions in the lung's ability to move and exchange gas can be measured by formal pulmonary function tests (PFTs).

Recent meta-analyses have shown that patient-related adverse risk factors for radiation pneumonitis among patients with non–small-cell lung cancer include older age,[129,130] history of chronic lung disease or diabetes,[131] and low preradiotherapy lung function.[131] Smoking was an adverse risk factor in one meta-analysis,[131] whereas not being an active or prior smoker[129] was an adverse risk factor in another, a discrepancy that is attributed to the complexity of the relationship between smoking, chronic lung disease, and pneumonitis.[131] Chemotherapy concurrent with radiation therapy,[131] particularly carboplatin/paclitaxel chemotherapy,[130] has been reported to increase the pneumonitis risk.

Cytokines appear to play a role (at least perhaps as a marker and maybe as a mediator) in the development of clinical radiation pneumonitis. Seminal work implicates transforming growth factor beta (TGF-β).[132,133] A powerful association between native circulating IL-1 and IL-6 levels and radiation pneumonitis have been reported from the University of Rochester.[134] A French study has also shown a correlation between circulating levels of IL-10 and IL-6 and the development of radiation pneumonitis.[135] Nevertheless, the literature reports in this area are not totally consistent. Cytokines may not be important for pulmonary fibrosis.[136] More recent data have also demonstrated pneumonitis risks correlated with polymorphisms of DNA repair[137-139] and TGF-β[140] genes correlating with pneumonitis risks. Positron emission tomography (PET) avidity of lung tissue after radiation has also been correlated with pneumonitis risk.[141]

Dose-Volume Data: Pneumonitis and Fibrosis

Several dosimetric parameters have been shown to be associated with the risk of radiation pneumonitis, including V5 to V70, mean lung dose (MLD), and model-based parameters.[142-146] These variables are correlated with each other, accounting for the fact that in most studies examining a range of *Vx* variables, many/most are significant.[147-161] The dosimetric parameters predictive of pneumonitis can also be used to predict fibrosis risks.[136] How normal lung is defined (i.e., lung minus gross target volume [GTV] or PTV) will affect the magnitude of the calculated dose-volume metrics.[162]

Table 14-2 summarizes many of the studies discussed here. Most of the published dose-volume data describes pneumonitis risks in patients with lung cancer, though data also exist for patients with breast cancer[150,163,164] and Hodgkin lymphoma.[165,166] In patients with Hodgkin lymphoma, pneumonitis risks appear to be lower for given dose-volume metrics that may relate to the younger age of this patient population.

An NTCP analysis from the Netherlands, in collaboration with the University of Michigan, suggests that using the MLD (linear function) is more predictive than using VX (step function).[150] However, V13 tended to be more predictive in situations where the MLD exceeded 20 Gy or V13 exceeded 50%. The TD50 values in this study were MLD of 30.8 Gy, V13 of >77%, and V20 of >65%, similar to the MLD of 31.8 Gy reported in a previous multiinstitutional study.[167] From an NTCP analysis from the Memorial Sloan Kettering Cancer Center (MSKCC),[148] a mean lung dose of ~26 Gy, V13 of >80% to ipsilateral lung, or V40 of >32% to lower lung results in a 50% risk of developing late complications. A mean lung dose of ~12 Gy or a V13 of >40% to ipsilateral lung results in a 5% late complication risk. A V13 of 36% of the lower lung, 42% of the total lung, or 62% of the ipsilateral lung results in a 20% risk of developing late grade ≥3 complications.

In a 1997 study from MSKCC, of patients treated with radiation alone, there was a significantly increased risk of grade ≥3 pulmonary toxicity, 38% with a V25 of >30% compared to 4% with a V25 of <30% ($p = 0.04$).[168] In subsequent studies from this same group, significant variables for predicting grade ≥3 pulmonary toxicity included mean lung dose, the range of V5 to V40 of total lung, V5 to V40 of ipsilateral lung, and V5 to V50 of lower lung.[148,153] The range of V5 to V20 ipsilateral lung was most predictive.

Investigators at Washington University also showed that the risk of pneumonitis significantly correlated with the V20; the 2-year incidence of grade ≥2 radiation was 36% versus 13% versus 7% versus 0% with a V20 of >40%, 32% to 40%, 22% to 31%, and <22% ($p = 0.0013$), respectively.[142] In another study from Washington University, radiation pneumonitis was significantly correlated with V5 to V80, with peak significance in the V5 to V15 and V70 to 75 ranges; radiation pneumonitis was also significantly correlated with the dose delivered to 5% to 100% of the lung (D5-100), with peak significance in the D30 to D40 and V90 to V95 ranges.[156]

In a 2001 study from Duke (in which 18% of patients received concurrent chemoradiotherapy) a V30 of >18% versus <18% was associated with a risk of grade ≥1 radiation pneumonitis of 24% versus 6% ($p = 0.0003$).[147] MLDs of <10 Gy, 10 Gy to 20 Gy, 21 Gy to 30 Gy, and >30 Gy were associated with risks of 10%, 16%, 27%, and 44%, respectively. A Japanese study of patients treated with platinum-based chemoradiotherapy found a 6-month risk of grade ≥2 radiation pneumonitis to be 85%, 51%, 18.3%, and 8.7% ($p < 0.0001$) with a V20 of ≥31%, 26% to 30%, 21% to 25%, and ≤20%, respectively.[169] In a University of Michigan study, a 10% risk for grade ≥2 pneumonitis and fibrosis was associated with a V20 >30% and an MLD >20 Gy. These thresholds provided a positive predictive value of 50% to 71% and a negative predictive value of 85% to 89%.[170] In a study from MDACC, the mean lung dose and V5 V65 were highly correlated with risk of pneumonitis, and V5 was the most significant factor in a multivariate analysis.[155] For a V5 ≤42% versus >42%, the risk of grade ≥3 pneumonitis at 1-year was 3% versus 38% ($p = 0.001$). In a Mayo Clinic study, V10 to V13 were most predictive of radiation pneumonitis; a V10 of 32% to 43%, V13 = 29% to 39%, V15 = 27% to 34%, and V20 of 21% to 31% resulted in a 10% to 20% risk of pneumonitis.[160] From a recent meta-analysis of 836

TABLE 14-2 Summary of Selected Studies Analyzing Dose-Volume Parameters Predictive of Lung Toxicity

Author, Year (*Center*)	Patient Population	Endpoint	Subgroup	Toxicity Rate
Seppenwoolde, 2003 (*van Leeuwenhoek Hosp.*)	Breast cancer, lymphoma, non–small cell lung cancer	Radiation pneumonitis	MLD = 31.8 Gy V13 = 77% V20 = 65%	50% (NTCP) 50% (NTCP) 50% (NTCP)
Yorke, 2002 *(MSKCC)*	Non–small cell lung cancer	Acute grade ≥3 pulmonary toxicity	MLD = 25 Gy MLD = 12 Gy V13 = 42% V13 (ipsilateral lung) = 80% V13 (ipsilateral lung) = 62% V13 (ipsilateral lung) = 40% V40 (lower lung) = 32% V13 (lower lung) = 36%	50% (NTCP) 5% (NTCP) 20% (NTCP) 50% (NTCP) 20% (NTCP) 5% (NTCP) 50% (NTCP) 20% (NTCP)
Armstrong, 1997 *(MSKCC)*	Non–small cell lung cancer	Acute grade ≥3 pulmonary toxicity	V25 > 30% V25 < –30%	38% 4%
Graham, 1999 (*Washington Univ.)*	Non–small cell lung cancer	Grade ≥3 radiation pneumonitis	V20 > –40% V20 = 32%-40% V20 = 22%-31% V20 < –22%	36% 13% 7% 0
Hernando, 2001 (*Duke Univ.*)	Non–small cell lung cancer, small-cell lung cancer	Grade ≥1 radiation pneumonitis	V30 > –18% V30 < –18% MLD <10 Gy MLD 10-20 Gy MLD 21-30 Gy MLD >30 Gy	24% 6% 10% 16% 27% 44%
Tsujino, 2003 (*Hyogo Medical Center*)	Non–small cell lung cancer	Grade ≥2 radiation pneumonitis	V20 ≤20% V20 = 21%-25% V20 = 26%-30% V20 ≥31%	9% 18% 51% 85%
Kong, 2006 (*U. Michigan)*	Non–small cell lung cancer	Grade 2 radiation pneumonitis	V20 > –30% MLD > –20 Gy	10% 10%
Wang, 2006 (*MDACC)*	Non–small cell lung cancer	Grade ≥3 radiation pneumonitis	V5 ≤42% V5 >42%	3% 38%
Koh, 2006 (*Princess Margaret H)*	Hodgkin lymphoma	Grade ≥2 radiation pneumonitis	V20 >40% V20 ≤40%	25% 0%
Schallenkamp, 2007 (*Mayo Clinic)*	Non–small cell lung cancer, small cell lung cancer	Grade ≥2 radiation pneumonitis	V10 = 32%-43% V13 = 29%-39% V15 = 27%-34% V20 = 21%-31%	10%-20% 10%-20% 10%-20% 10%-20%
Mazeron, 2010* (*U Lyon)*	Non–small cell lung cancer	Radiation fibrosis	V10 <33% V20 <18% V30 <13% V40 <10% V50 <5% V10 >33% V20 > 8% V30 >13% V40 >10% V50 >5%	11% 13% 14% 14% 13% 26% 24% 23% 23% 24%
Ramella, 2010* (*Rome, Italy)*	Non–small cell lung cancer	Grade ≥2 radiation pneumonitis	ipsilateral V20 ≤52% ipsilateral V30 ≤39% ipsilateral MLD ≤22 Gy ipsilateral V20 >52% ipsilateral V30 >39% ipsilateral MLD >22 Gy	9% 8% 7% 46% 38% 23%
Fox, 2012* (*Brigham and Women's H)*	Hodgkin lymphoma	Grade ≥2 radiation pneumonitis	V20 ≥33.5% V20 <33.5% MLD >13.5 Gy MLD <13.5 Gy	21% 2% 19% 4%

TABLE 14-2 Summary of Selected Studies Analyzing Dose-Volume Parameters Predictive of Lung Toxicity—cont'd

Author, Year (*Center*)	Patient Population	Endpoint	Subgroup	Toxicity Rate
Meta-analysis, 2013*	Non–small cell lung cancer	Grade ≥ radiation pneumonitis	V20 <20%	18.4%
			V20 = 20%<30%	30.3%
			V20 = 30%<40%	32.6%
			V20 >40	35.9%
	Non–small cell lung cancer	Fatal (grade 5) radiation pneumonitis	V20 <20%	0%
			V20 = 20%<30%	1.0%
			V20 = 30%<40%	2.9%
			V20 >40	3.5%

NTCP, *Normal tissue complication probability modeling.*
**Published after QUANTEC review.*

patients, lung V20 of <20%, 20 to <30%, 30 to <40%, and >40% were associated with symptomatic pneumonitis risks of 18.4%, 30.3%, 32.6%, and 35.9%, respectively, and fatal pneumonitis risks of 0%, 1.0%, 2.9%, and 3.5%, respectively.[130]

Several dose escalation studies have used V20, V_{eff} or NTCP to allocate patients into given dose levels.[171-174] In the RTOG 93-11 dose escalation study, patients with a V20 of <25% experienced a 7% to 16% 18-month actuarial rate of grade ≥3 late lung toxicity with prescribed doses of 70.9 Gy to 90.3 Gy; the absolute risk of grade ≥2 late lung toxicity was 30% to 45%, with one fatal lung complication at the 90.3-Gy dose level. Patients with a V20 of 25% to 36% treated to doses of 70.9 Gy to 77.4, Gy experienced 15% grade ≥3 late toxicity at 18 months, and an absolute risk of grade ≥2 late lung toxicity of 40% to 60%.[171] D15 was the most predictive variable for radiation pneumonitis.[159]

In Dutch study, the effect of regional dose on the lung was investigated, with the lung divided into: central and peripheral; ipsilateral and contralateral; caudal and cranial; and anterior and posterior subvolumes.[175] The mean regional dose to the posterior, caudal, ipsilateral, central, and peripheral lung subvolumes significantly correlated with the incidence of steroid-requiring radiation pneumonitis; caudal location was correlated with greater pneumonitis risks, whereas no statistical difference in risks were observed between anterior and posterior locations or central and peripheral locations. In a similar study from MSKCC, the risk of radiation pneumonitis was better correlated with the radiation dose to the inferior aspect of the lung, rather than the superior aspect.[148]

Tumor location in the lower lung also appears to be an adverse factor affecting risk of pneumonitis in patients with lung cancer.[129-131] In the aforementioned study from Washington University,[156] inferior tumor location was the most significant predictor of radiation pneumonitis. Tumor location was not a strong correlate to radiation pneumonitis in a study from patients treated on RTOG 93-11, perhaps attributable, in part, to differences in treatment (with RTOG 93-11 designed to treat smaller volumes to higher doses) and differences in tumor size and location (the RTOG 93-11 tumors tended to be smaller and more superiorly located).[159] Using a combined data set of patients from RTOG 93-11 and Washington University, tumor location, in addition to MLD were significant. In a recent Washington University study of 209 patients, cardiac dose, specifically V65 and D10, was more predictive of radiation pneumonitis than lung dose-volume metrics; the reason is unknown and the authors demonstrate that that heart variables are not simply surrogates for lung variables.[176]

For some patients with advanced stage non–small-cell lung cancer, IMRT yields unique dose distributions, with improved target conformality and increased (albeit modest) target heterogeneity.[177] The IMRT-based dose distributions appear to reduce the risk of normal tissue injury in patients with non–small-cell lung cancer. Investigators at MDACC compared their rates of lung toxicity in patients with treated IMRT versus 3D planning and noted a reduction in toxicity with the IMRT approach.[178] Investigators at MSKCC noted a similarly low rate of clinical lung injury in patients with non–small-cell cancer treated with IMRT.[179] In the MDACC study, a V5 >70% was associated with a 21% risk of grade ≥3 pneumonitis versus a 2% risk with a V5 ≤70% (p = 0.017). Proton therapy also allows for reduction of lung volume receiving a given dose, and data are emerging on its utility.

IMRT has also been used to treat patients with mesothelioma. In a study from Dana Farber, in which patients received thoracic IMRT after pneumonectomy for mesothelioma, 6 of 13 patients developed fatal pneumonitis.[180] The median V20, V5, and MLD for patients who developed pneumonitis was 17.6%, 98.6%, and 15.2 Gy, respectively, versus 10.9%, 90%, and 12.9 Gy for those who did not develop pneumonitis. Although these differences were not significant, the severity of the toxicities merits caution in treating patients to large volumes after a pneumonectomy. In a study from Duke, 1 of 13 patients treated with IMRT for mesothelioma died from pneumonitis, and 2 others developed symptomatic pneumonitis.[181] The median V20, V5, and MLD for patients developed pneumonitis was 2.3%, 92%, and 7.9 Gy, respectively, versus 0.2%, 66%, and 7.5 Gy for those who did not develop pneumonitis, versus 6.9%, 92%, and 11.4 Gy for the patient who developed fatal pneumonitis. In a study of mesothelioma patients from MDACC, 6 of 63 patients died from pulmonary-related causes (including 2 patients with fatal pneumonitis).[182] The V20 was significant on univariate and multivariate analyses (p = 0.017), with a V20 >7% corresponding to a 42-fold increase in the risk of pulmonary death.

Summary and Other Key Points from QUANTEC Review[183]

A variety of studies note a dose-response relationship for a variety of metrics predictive of radiation pneumonitis. The QUANTEC review pooled the data from many centers. This shows that there is no specific threshold for pneumonitis, with risks increasing gradually with increased dose. Because many dose/volume parameters of the lung (i.e., V5 through V30, MLD) are correlated with each other, there likely is not an "optimal" parameter. For patients with non–small-cell lung cancer, it is prudent to limit the V20 to <30% to 35%, and the mean lung dose to <20 Gy to 23 Gy, to limit the risk of pneumonitis to less than 20%. In patients irradiated postpneumonectomy for mesothelioma, it is prudent to limit the V5 <60%, the V20 <4% to 10%, and the mean lung dose to <8 Gy. Radiation-induced pneumonitis appears more commonly in

patients with lower- versus upper-lobe tumors and may be better correlated with radiation doses to the lower versus upper lung. The cause of this correlation is unknown and requires further investigation. Perhaps it is related to differences in ventilation and perfusion of different lung regions.

Dose-Volume Data: Pulmonary Function

The majority of studies have considered shortness of breath as the relevant endpoint. This is what is typically recorded in patient records, and, from the patient's perspective, perhaps the most meaningful endpoint. However, symptoms can be non specific and difficult to quantify. Therefore, investigators have also considered more specific and objective endpoints such changes in PFTs and imaging.

Changes in PFTs following thoracic radiation reflect a combination of improvements because of tumor shrinkage (typically acutely), and declines because radiation-induced injury (both acute and chronic).[184] Several studies have noted long-term declines in PFTs following thoracic radiation,[185-187] although changes can be transient.[188] The association between shortness of breath following radiation and declines in PFTs is complex.[189] Duke University studies have shown a correlation between V30 and NTCP with changes in forced expiratory volume in 1 second (FEV1) and diffusion capacity (DLCO).[190] The University of Michigan investigators, however, did not find any correlation of V20, MLD, or V_{eff} with changes in FEV1 or DLCO.[191] Attempts have been made to model the risk of changes in PFTs,[192,193] though certainly this is a complicated area of study. Recent data from MDACC suggest that severity of pneumonitis is correlated with reduction in DLCO.[194]

Similarly, imaging tests provide clear objective metrics. Several studies have noted an association between regional radiation doses and changes in regional imaging tests (CT-defined density or single-photon emission computed tomography [SPECT]-defined perfusion/ventilation).[195-198] The extent or severity of these imaging changes is related to changes in global lung function (assessed as either symptoms or changes in PFTs), but the correlations are relatively weak.[184,192,193,198]

Summary and Other Key Points from QUANTEC Review[183]

For pulmonary function, it appears that minimizing the V30 minimizes risk of decline in pulmonary function test parameters, though, as is the case with pneumonitis, other dose-volume measures may be predictive as well. The study of radiation-induced lung injury is confounded by the use of ambiguous endpoints, as well as toxic exposures (e.g., smoking) and treatment with chemotherapy (e.g., bleomycin and cisplatinum). Many toxicity scoring systems combine radiologic, functional, and symptomatic criteria in their grading system. However, each pulmonary toxicity endpoint may have different dose/volume dependence, and future studies should be explicit in defining endpoints.

HEART

Organ Function and Clinical Significance

The heart is the muscular organ, located in the left hemithorax (with the rare exception of dextrocardia) which, via continuous rhythmic contraction, pumps blood throughout the blood vessels. The functional and structural complexity of the heart places it at risk for a spectrum of radiation and chemotherapy injuries that can manifest months to years following therapy. All components of the heart and the surrounding pericardium are susceptible to radiation damage. Radiation-induced cardiac injury includes pericarditis, congestive heart failure, restrictive cardiomyopathy, valvular insufficiency and stenosis, coronary artery disease, ischemia, and infraction. A history of anthracycline chemotherapy can exacerbate radiation-elated cardiac toxicity.

Dose-Volume Data

Abundant studies have demonstrated an increased risk of cardiac morbidity following left-sided thoracic radiation versus right-sided thoracic radiation in patients irradiated for breast cancer. It is well accepted that reducing the dose prescribed to the mediastinum and reducing the volume of heart in the radiation field reduces the risk of late toxicity.[199-201] Studies from Duke demonstrated that an increased percentage of the left ventricle irradiated correlates with a greater risk of cardiac perfusion defects.[202-204] Even over the range of low dose exposure (~8 Gy to 20 Gy) to small volumes of the cardiac apex, an increased risk of heart disease has been reported.[205]

A study from Stockholm used normal tissue complication probability modeling to predict the risk of late heart toxicity in women treated for breast cancer.[206] In their models, the TD50 was optimized to a value of 52 Gy to the myocardium. A 5% risk of excess cardiac mortality at 15 years was associated with a myocardial dose of ~30 Gy, a V33 of >60%, V38 of >33%, or a V42 of >20%. Calculations using the whole heart volume (as opposed to myocardium) yielded similar values.

The same group from Stockholm used a similar analysis to assess cardiac risk in patients with Hodgkin disease.[207] Patients were stratified into two risk groups: those with a V38 of >35% and those with a V38 of <35%. The excess mortality risk at 15 years was 7.9% and 4.7%, respectively. The TD50 was calculated to be 70 Gy. A heart dose of 42 Gy resulted in a 5% normal tissue complication probability, whereas a heart dose of 53 Gy resulted in a 10% NTCP. The corresponding values in the patients with breast cancer were 37 Gy and 44 Gy respectively (lower threshold doses and steeper gradient). The differences in complication probabilities and TD50 between the breast and Hodgkin disease cohorts suggest that radiation exposure to different portions of heart results in differences in cardiac risk,[207] though there may be other confounding variables not easily identified (e.g., patient age at treatment, similar risk factors between breast cancer and cardiac disease, etc.)

Mean heart dose to the left ventricle, both ventricles, or whole heart were not predictive for cardiac toxicity in a study of 328 survivors of non–small-cell lung cancer.[208] A Wayne State University study of 102 survivors of esophageal cancer, demonstrated thresholds for symptomatic cardiac toxicity to be heart V20, V30, and V40 above 70%, 65%, and 60%, respectively.[209]

A recent landmark Swedish/Danish study analyzed 960 survivors of breast cancer who experienced major coronary events and 1,205 controls, treated from 1958 to 2001.[210] The authors showed a linear relationship with mean heart dose and coronary events, with the risk being increased by 7.4% per Gy with no apparent threshold and persisting decades after treatment. The concept of no-threshold dose conflicts with our historical understanding (that "low doses" were likely inconsequential) as well as a recent University of Michigan study looking at myocardial perfusion scans after low-dose exposure (average heart mean dose <5 Gy) in patients with breast cancer; the authors found no correlations between cardiac doses and assessed cardiac function.[211] A potential criticism of the Swedish/Danish study is that radiation fields were reconstructed using a CT scan of a "typical woman" to generate DVH information. This undoubtedly introduced uncertainties

in their analysis that are acknowledged by the authors. Nevertheless, this was really the best that could humanly be done because the patients were treated in the pre-3D planning era. The investigators performed in-depth dosimetric reconstructions based on the available information.

The lack of a dose threshold might be related in part to the techniques used and potential differences between the delivered and planned doses. Radiation is delivered in daily fractions over many weeks. Inter- and intrafraction variations (e.g., because of daily set-up and motion from breathing) result in differences between the planned and delivered dose. The planned dose is *not* necessarily a good representation of the "average" of the delivered fractions, particularly for patients with a low planned mean heart dose. Such a patient likely has a beam edge close to, or encroaching to a small degree on, the heart. Because the dose gradient is steep near the beam edge, setting-up the beams too deep will markedly increase the cardiac dose. Setting them up too shallow does *not* yield a corresponding decrease in dose, because if the planned dose is already low, one cannot reduce dose appreciably lower. Thus, although set-up irregularities *might* be geometrically equally distributed relative to the planning scan, the dosimetric effects are not symmetrical, and such set-up variations often tend to *increase* the cardiac exposure. This might, to some degree, explain the low-dose effects seen by Darby.[212]

The findings from Darby et al may not be necessarily applicable to women treated with modern radiation planning and deliver methods because the doses are far lower, and the set-up techniques are likely more robust. In fact, the lead author previously showed no increase in cardiac mortality among women treated with radiotherapy after 1992 in the United States.[213] Nevertheless, the recent Darby study is a reminder that radiation-induced cardiac injury is a serious consideration.

In the Darby study, the mean heart dose was as good (or better) a predictor of risk than doses to the coronary arteries. This is surprising because the coronary arteries are often implicated as the main target for radiation-associated heart injury. Darby's observation may be the result of uncertainties in their estimation of coronary artery doses. Nevertheless, several studies note reduced perfusion in irradiated cardiac regions that do *not* correspond to a coronary artery's territory,[202] thus implicating microvascular injury as a potential mechanism for radiation-associated heart injury and an endpoint more plausibly associated with mean dose. The mean heart dose is likely largely a surrogate for dose to critical substructures such as the left-ventricular muscle and arteries.[212]

In another Swedish study, which correlated angiography findings with coronary artery dose-exposure extrapolated from the radiation treatment fields, an approximate twofold increase risk in high-grade coronary artery stenosis was found in women who received high-risk radiotherapy (i.e., specific coronary arteries were exposed to the highest radiation doses during breast cancer radiotherapy).[214] Furthermore, stenosis in these high-risk patients was more likely to occur in irradiated regions, specifically the right coronary artery (not accounted for[215] in the Swedish/Danish study) and distal left anterior descending artery.

There is little data on correlating heart dose-volume metrics with subsequent ejection fraction. In a study of patients with esophageal cancer treated with chemoradiation at Roswell Park Cancer Institute, the radiation dose to heart, left ventricle, and left anterior descending artery (quantified as V20 to V40) were not clinically or statistically associated with changes in the ejection fraction (albeit in a small study, with limited follow-up).[216] The aforementioned University of Michigan study likewise did not show a dose correlation with ejection fraction.[208]

A study from MDACC described the risk of pericardial effusions in patients treated for esophageal cancer.[217] A mean dose >26 Gy and relative volumes of the pericardium treated to doses greater than 3 Gy to 50 Gy (rV3 to rV50) was associated with effusions, with the strongest association being rV30. At 18 months postradiation, for a rV30 of >46% versus <46%, the rate of pericardial effusion was 73% versus 13% (p = 0.001); for a mean pericardium dose >26 Gy versus <26 Gy, the rate of pericardial effusion was 73% versus 13% (p = 0.001). A study from the University of Michigan also demonstrated that a mean dose >27 Gy and maximum dose 47 Gy correlated with risk of pericardial effusion; however, only patients treated with 3.5 Gy fractions developed pericardial effusions.[218]

Radiotherapy has been associated with valvular heart disease.[219] The incidence has been related to mediastinal radiation doses >30 Gy and younger age at irradiation. Subclinical valvular disease has been detected at 2->20 years postradiation,[219] but it appears to take much longer for clinical symptoms to become apparent (median interval 22 years from radiation to symptoms). For patients receiving radiation for Hodgkin lymphoma, at a median of >10 years after radiation aortic valvular disease usually consists of mixed stenosis and regurgitation and is more common than mitral and right-sided valvular disease.[219,220] From NTCP modeling of radiation-induced asymptomatic heart valvular defects, among 20 of 56 survivors of Hodgkin lymphoma, the cardiac chamber (left ventricle and left atrium) V30, cardiac chamber volume, and lung volume were predictive.[221]

Antracyclines and Other Risk Factors

In patients with Hodgkin disease, radiation exposure, in conjunction with anthracyclines, may impair ejection fraction and increase risk of myocardial infarction, congestive heart failure, and valvular disorders. Data on the combined effects of anthracycline and radiation remain sparse. A report of 1474 survivors of Hodgkin lymphoma younger than 41 years at treatment and followed for a median of 18.7 years has shed some light.[222] Risks of myocardial infarction and congestive heart failure were significantly increased, with standard incidence ratios of 3.6 and 4.9, respectively for survivors of Hodgkin lymphoma versus the general Dutch population. Mediastinal radiation alone increases the risks of myocardial infarction, angina pectoris, congestive heart failure, and valvular disorders (two- to sevenfold). The addition of anthracyclines further elevated the risks of congestive heart failure and valvular disorders from mediastinal radiation, with hazard ratios of 2.81 and 2.10, respectively. The 25-year cumulative incidence of congestive heart failure following combined radiation and anthracycline chemotherapy was 7.9%.

Other risk factors for cardiac disease, particularly coronary artery disease, must be considered. For example, data from the University of Rochester assessed the risk of coronary artery disease in survivors of Hodgkin lymphoma and also the prevalence of cardiac risk factors. The relative risk of cardiac death was 3.1 for males versus 1.8 for females. Other risk factors were more common than in the general population; among patients with Hodgkin lymphoma experiencing morbid cardiac events, 72% smoked, 72% were male, 78% had hypercholesterolemia, 61% were obese, 28% had a positive family history, 33% had hypertension, and 6% had diabetes.[223]

Summary and Other Key Points from QUANTEC Review[224]

The substructures of the heart, as well as the intersection of the heart and great vessels can be challenging to differentiate with

axial CT imaging, and the heart border is often difficult to differentiate from the adjacent liver and diaphragm. The heart moves with the respiratory and cardiac cycles, with different regions moving to different degrees. Several clinical factors, such as increasing age, comorbidities, and anthracycline exposure, appear to increase the risk of radiation-induced injury. Whereas based on limited data, there appears to be a dose or volume dependence for pericardial disease, cardiac mortality, and perfusion abnormalities. A heart V30 of >45% and a mean cardiac dose of >26 Gy are associated with a higher risk of pericarditis. A heart V30 to V40 of ~30% to 35% is associated with a ~5% excess risk of cardiac death at ~15 years. These dose-volume metrics likely oversimplify risk estimates related coronary artery disease, which are probably best correlated with high dose (>50 Gy) to small volumes of coronary artery.[215] In patients with breast and lung cancer, it is recommended that the irradiated heart volume be minimized as much as possible degree without compromising target coverage. In patients with lymphoma the whole heart should be limited to <30 Gy if the patient is treated with radiation alone, and 15 Gy for those also receiving anthracycline chemotherapy.

GASTROINTESTINAL SYSTEM: ESOPHAGUS

Organ Function and Clinical Significance

The esophagus is the muscle lined organ that allows and facilitates the transit of solids and liquids from the mouth to the stomach. The esophagus is a moveable (slightly), hollow, distensible organ. On CT images, the cross-sectional esophageal area/volume is highly variable. This may not accurately reflect the true anatomy of the organ. In gross esophageal specimens, the cross-sectional area of the esophagus is fairly uniform at all axial levels.[225]

Acute esophagitis is common, and is often severe, in patients receiving radiation for thoracic malignancies (e.g., esophageal cancer, primary lung cancer). Some patients may require a feeding tube or treatment interruptions due to acute esophagitis. Because most patients with thoracic cancers have a poor prognosis, acute toxicity may be considered more clinically relevant than late injury. Late esophageal complications include dysphagia, stricture, dysmotility, odynophagia, and rarely necrosis or fistula.

Dose-Volume Data

In a series from Washington University, grades 3 to 5 esophageal toxicity (acute and late) was associated with a maximal dose (*Dmax*) of >58 Gy, a mean dose of >34 Gy and the administration of concurrent chemotherapy.[226] The V55 was not significant. A Chinese study reported that maximal dose >60 Gy, as well as the use of concurrent chemotherapy were significant factors for esophageal toxicity (acute and late).[227] In a series from Duke University, the V50, the surface dose receiving ≥50 Gy (S50), the length of esophagus receiving >50 Gy to 60 Gy, and a circumferential *Dmax* >80 Gy were significant predictors of late esophageal toxicity.[228] A V50 of >32% or an S50 of >32% resulted in crude rates of ~30% late esophageal toxicity versus 7% below these thresholds ($p = 0.02$ and 0.04, respectively). With >3.2 cm of the esophagus receiving >50 Gy, late toxicity occurred in ~30% versus 4% in those with <3.2 cm receiving >50 Gy ($p = 0.008$). In another series from Duke, late grade ≥1 toxicity was correlated with several dose parameters: the entire circumference receiving ≥50 Gy and ≥55 Gy; 75% of the circumference receiving ≥70 Gy; and maximal percentage of circumference receiving ≥60 Gy to 80 Gy.[229] The rate of grade ≥1 late toxicity was ~5% in patients with a V50 to V70 of 0% to 30% versus ~25% in those with a V70 of 31% to 64% and ~10% in those with a V50 >60% (nonsignificant). Acute esophageal toxicity was the greatest predictor of late toxicity. In two studies, most of the patients who developed late grade ≥3 toxicity had developed acute grade ≥3, though roughly 25% to 40% of patients who developed grade ≥3 late toxicity had only grades 0 to 2 acute esophageal toxicity.[226,227]

From the data analyzed for QUANTEC, several studies noted an increased risk with increasing dose/volume parameters. However, because different studies considered different variables, optimal dose/volume predictors were considered elusive. Further, because different dose/volume parameters are correlated to each other, it may be that there are no true "optimal" parameters and that alternative predictive models will be equally useful. From a 2013 meta-analysis of 1082 patients treated with chemoradiation for non–small-cell lung cancer, esophageal V5 to V70 parameters (in 5-Gy increments) were all significant predictors of grade ≥2 esophagitis; on multivariate analyses V60 proved to be the most significant predictor of grades ≥2-3 esophagitis.[230] Recursive partitioning identified three risk groups: low (29% and 4% risk of grades ≥2 and ≥3 esophagitis with V60 <0.07%), intermediate (41% and 10% risk of grade ≥2 and ≥3 esophagitis with V60 ≥0.07% to 17%), and high (59% and 22% risk of grades ≥2 and ≥3 esophagitis with V60 ≥17%). These authors did not consider dose-surface metrics or esophageal length or circumference.

Summary and Other Key Points from QUANTEC Review[231]

The esophagus can be difficult to differentiate from surrounding soft tissues. Acute esophageal injury is much more common, and thus most studies have explicitly analyzed acute toxicity (which is not explicitly reviewed here). For acute and late injury, there is a dose response for a variety of threshold volumes (V20 to V70). A *Dmax* >55Gy to 60 Gy as well as esophageal surface, volume, length, and circumference receiving >50 Gy to 60 Gy appear to correlate with toxicity. Acute esophageal toxicity can result in late toxicity. It was not possible to identify a single-best threshold volumetric parameter for esophageal irradiation because a wide range of dose-volume parameters correlate with toxicity. Based on the RTOG 0617 dose escalation study for non–small cell lung cancer, it was suggested that the mean dose to the esophagus be kept <34 Gy; in that study, the esophageal V60 will also be reported. A recent meta-analysis suggests that V60 is most predictive for esophagitis.

GASTROINTESTINAL SYSTEM: STOMACH AND SMALL BOWEL

Organ Function and Clinical Significance

The stomach and small bowel aid in the digestion and absorption of food and nutrients. Symptoms from radiation-related late toxicities include dyspepsia, gastric ulceration, diarrhea, bowl obstruction, and bowel ulceration, fistula, or perforation. The primary long-term endpoints considered for the small bowel are stricture and diarrhea. For the stomach, perforation and ulceration are commonly considered. Several patient-related variables, such as history of diabetes, age, race, body habitus, and prior surgery, likely impact the risk of late toxicity.[232] Because stomach and small bowel are mobile and distensible, determining accurate dose-volume (or dose-surface) constraints are challenging. Factors affecting risk of late toxicity include total dose (with doses in excess of 40 Gy to 50 Gy increasing the risk of late complications), fractional dose, prior abdominal surgery (which increases the risk of bowel obstruction), and concurrent chemotherapy use.

Dose-Volume Data

Dose

Late radiation induced stomach injury has been reported to occur with increasing frequency with increasing doses. In a study from Walter Reed, the rates of gastric ulceration were 4% and 16% after treatment of <50 Gy versus >50 Gy. Similarly, the rates of perforation were 2% and 14% in the same dose cohorts. Overall, the dose of approximately 50 Gy to the stomach was associated with about a 2% to 6% incidence of severe late injury. The volume affect for late stomach injury is not well defined. For late small bowel toxicity, a dose of approximately 50 Gy is associated with obstruction or perforation rates that are approximately 2% to 9%. Prior abdominal surgery appears to increase the risk of late small bowel injury following radiation. In the European Organization for Research and Treatment of Cancer (EORTC) study, the rate of complications was 3% without prior abdominal surgery versus 12% with prior abdominal surgery.[233]

Dose Volume

There is a paucity of good quantitative data on dose-volume metrics that predict for gastric or bowel late toxicity. Nevertheless, there are data that demonstrate a volume effect. The risk of bowel obstruction among patients with rectal cancer whose fields extended to L1 or L2 was 30% versus 9% in those treated with pelvis only fields.[234] The University of Michigan investigated gastric and duodenal bleeding after radiation of patients with liver tumors.[235] Normal tissue complication modeling was consistent with a dose threshold (~60 Gy) for bleeding without a large volume effect.

A few studies published after QUANTEC correlated small bowel toxicity risks with dose-volume metrics. In a study of 46 patients with locally advanced pancreatic cancer, treated with concurrent gemcitabine and radiotherapy, duodenal V35 >20% was associated with a 41% risk of grade ≥3 small bowel toxicity (acute or late), versus 0% for a V35 <20%.[236] In another study of patients with locally advanced pancreatic cancer (n = 106), in which V40 to V60 was analyzed, a V55 ≥1 mL versus < 1 mL was significantly correlated with grade ≥2 toxicity (47% versus 9%, p = 0.0003).[237] In a study of 46 women treated with extended field radiation for gynecologic malignancies up to 65 Gy, only three patients experienced acute grade ≥3 gastrointestinal toxicity and thee patients experienced late grade ≥3 gastrointestinal toxicity (none of which was duodenal toxicity); V5 to V65 did not correlate with toxicity risks.[238] From a recent systematic review of women undergoing extended field radiation, a point maximum of 55 Gy to small bowel was estimated to yield a 10% toxicity risk within 5 years.[239]

Summary and Other Key Points from QUANTEC Review[240]

The stomach and the intestines are mobile structures with definite inter- and intrafraction motion. This makes some of the doses/volumes/outcomes data less certain. Two different approaches have been considered when defining small bowel volumes. Either the entire potential space of small bowel-containing volume (i.e., incorporating all regions where bowel can be situated),[241] or the actual visualized loops of bowel on the planning CT[242] can be considered as an organ at risk. Using the entire potential small bowel space, it is suggested that the small bowel exposed to V45 to V50 should be less than 195 cc to reduce acute toxicity (not discussed previously)[241]; while using the visualized loops of bowel, it is recommended that the V15 should be less than 120 cc.[242] A study (with neoadjuvant radiation for rectal cancer) published after QUANTEC predicts a 10% risk of grade ≥3 small bowel toxicity with a V15 <275 cc for contoured bowel loops and <830 cc for the peritoneal space.[243] Although these dose constraints were derived from acute toxicity data, they do provide guidelines that should help minimize risk of late toxicity as well. For the stomach, it is recommended to maintain the dose to the whole stomach to <45 Gy; a maximum point dose might be an important predictor of toxicity, but more data are needed to confirm this hypothesis.

GASTROINTESTINAL SYSTEM: RECTUM

Organ Function and Clinical Significance

The rectum is the terminal portion of the large intestines that functions as a temporary storage for feces, as well as providing the urge to defecate. The most common late radiation related rectal complication is bleeding. Rectal ulceration and fistula are much less common. Other late injuries include stricture and decreased rectal compliance, which can result in frequent small stools. The anus is also at risk of late complication including stricture and laxity, leading to fecal incontinence. Patients are at a higher risk of late rectal sequelae, including gastrointestinal bleeding, proctitis, diarrhea, and tenesmus, with higher maximal and mean rectal doses. Several patient-related variables, such as history of diabetes or vascular disease, inflammatory disease, and age may impact the risk of late toxicity.[232,244-246] Acute bowel toxicity appears to be correlated with late proctitis and increased stool frequency.[246] Prior abdominal surgery is also relevant.[247] An XRCC1 polymorphism has also been implicated as a risk factor for late rectal toxicity.[248]

Dose-Volume Data

Abundant dosimetric data has shown a correlation of risk with rectal volume and surface/rectal wall doses.[249-264] Table 14-3 summarizes many of these studies, also discussed here.

MSKCC has shown a significant difference in the DVHs between patients who developed rectal bleeding versus those who did not after conformal radiation for prostate cancer.[249] The percentage of rectum exposed to 62% and 102% of the prescription dose (70.2 Gy or 75.6 Gy) was significant; the rectal wall being encompassed by the 50% isodose line, higher maximal dose to the rectum, and smaller rectal volume were also significantly adverse risk factors.[249,250] In a study of 1571 patients treated at MSKCC, the use of IMRT and the lack of acute rectal toxicity predicted for lower risk of late rectal toxicity.[251]

An Austrian study found that a V59 of ≥57% resulted in increased grade 2 rectal toxicity (31% versus 11%, p = 0.003).[252] Two Italian multicenter studies found a significant dose volume effect from V50 to V70, with suggested cutoff values of V50 ≤60% to 65%, V60 ≤45% to 50%, and V70 ≤25% to 30%; the risk of grade ≥2 rectal complications was ~4% to 8% versus ~20% to 30% risk above and below the cutoff values.[253,254] A rectal volume <55 mL was also a significant risk factor for late bleeding. In the postprostatectomy setting, this Italian group demonstrated that a mean rectal dose ≥54 Gy, V50 ≥63%, V55 ≥57%, V60 ≥50%, and rectal volume <60 mL were predictive of late bleeding.[255]

In a randomized trial of 70 Gy versus 78 Gy from MDACC in the treatment of early- to intermediate-risk early stage prostate cancer, the risk of late grade ≥2 rectal complications was significantly greater with a rectal V70 ≥25% versus V70 <25% (46 versus 16%, p = 0.001).[256] A retrospective analysis from MDACC showed that the risk is a continuous function of dose and volume, with suggested cut-off points for lowering the

TABLE 14-3 Summary of Selected Studies Analyzing Dose-Volume Parameters Predictive of Rectal Toxicity

Author, Year (*Center*)	Patient population	Endpoint	Subgroup	Toxicity Rate
Wachter, 2001 (*Univ. Hosp. Vienna*)	Prostate cancer	Grade 2 Rectal toxicity	V59 ≥57% V59 <57%	31% 11%
Fiorino, 2002, 2003 (*Hosp. San Raffaele*)	Prostate cancer	Grade 2 Rectal toxicity	V50 ≤60%65% V60 ≤45%-50% V70 ≤25%-30% V50 >65% V60 >50% V70 >30%	4%-8% 4%-8% 4%-8% 20%-30% 20%-30% 20%-30%
Cozzarini, 2003 (*Hosp. San Raffaele*)	Prostate cancer s/p prostatectomy	Late rectal bleeding	Mean rectal dose ≤54 gy V50 ≤63% V55 ≤57% V60 ≥50% Mean rectal dose <54 gy V50 <63% V55 <57% V60 <50%	7% 7% 7% 7% 22% 21% 21% 19%
Huang, 2002 (*MDACC*)	Prostate cancer	Grade ≥2 Rectal toxicity	V70 ≥ 26% V70 <26%	54% 13%
Peeters, 2006 (*van Leeuwenhoek Hosp.*)	Prostate cancer	Rectal bleeding Requiring laser treatment or packed red blood cells Use of incontinence pads	V65 = 7%-23% V65 = 23%-29% V65 = 29%-36% V65 >36% Anal mean <28 gy Anal mean 28 gy-38 gy Anal mean 38 gy-46 gy Anal mean >46 gy	<1% 4% 11% 10% <5% 7% 9% >20%
Boermsa, 1998 (*NKI*)	Prostate cancer	Rectal bleeding	Rectal wall v65 <40% Rectal wall v70 <30% Rectal wall v75 <5% Rectal wall v65 >40% Rectal wall v70 >30% Rectal wall v75 >5%	0% 0% 0% 10% 9% 9%
Kupelian, 2002 (*Cleveland Clinic*)	Prostate cancer	Rectal bleeding	Rectal wall v70-v78 <15 mL Rectal wall v70-v78 >15 mL	5% 22%
Vargas, 2005 (*William Beaumont*)	Prostate cancer	Grade ≥2 Rectal toxicity	V70 <25% V70 = 25%-40% V70 >40% Rectal wall v70 <5 mL Rectal wall v70 5 mL-15 mL Rectal wall v70 >15 mL Rectal wall v70 <25% Rectal wall v70 = 25%-40% Rectal wall v70 >40%	9% 19% 24% 8% 13% 32% 9% 18% 25%
Pederson, 2012* (*Univ. Chicago*)	Prostate cancer	4-Year Grade ≥2 Gastrointestinal toxicity	V70 ≤10% V65 ≤20% V40 ≤40% V70 ≤20% V65 ≤40% V40 ≤80% V70 >20% V65 >40% V40 >80%	0% 0% 0% 8% 8% 8% 15% 15% 15%

**Published after QUANTEC review.*

complication risk: V60 ≤41%, V70 ≤26%, V76 ≤16% or 3.8 mL and V78 ≤5% or 1.4 mL.[257] At 6 years, the risk of late grade ≥2 rectal complications was 54% for patients with a rectal V70 ≥26% versus 13% for a V70 <26%.

Among patients treated on the Dutch randomized trial of 68 versus 78 Gy,[245] the mean anal dose (as well as V5 to V60) significantly predicted the rate of grade ≥2 gastrointestinal toxicity (at 4 years, 16% versus 31% for a mean dose <19 Gy versus >52 Gy).[258] The mean dose (as well as V5 to V70) also predicted the risk for use of incontinence pads (at 5 years, <5% versus >20% for a mean dose <28 Gy versus >46 Gy). The anorectal V65 (as well as V55 to V60) was significantly predictive of rectal bleeding (4-year risk <1% and >10% for a V65 <23% versus >29%).[258]

The percentage of rectum or rectal wall receiving a given dose can be subjective (i.e., based on how much of the rectum

is segmented); using the absolute volume of rectum[262] or rectal wall is less subjective, though defining the rectal wall is not standardized. The rectum extends from the rectosigmoid junction to the anus, with the inferior extent generally defined as the level of the anal verge, above the anus, the ischial tuberosities or 2 cm below the ischial tuberosities. Dosimetric parameters of the rectal wall or rectal surface may be more predictive of some late toxicities.[265] William Beaumont Hospital demonstrated that the rectal volume as well as rectal wall V50 to V70 values predict late toxicity, with rectal wall being more predictive of grades 2 to 3 late effects; acute toxicity is also predictive of late toxicity.[259] MDACC has also shown rectal wall to be better predictive of late rectal bleeding.[260] From a 1998 Dutch study, recommendations for the volume of rectal wall exceeding 65 Gy, 70 Gy, and 75 Gy are <40%, <30%, and <5%, respectively.[261] Data from the Cleveland Clinic[262] and William Beaumont[259] showed a significantly increased risk of grade ≥2 rectal toxicity with rectal or rectal wall V70 to V78 of ≥15 mL versus <15 mL (~20% >30% versus ~5% to 10%).

More than a dozen NTCP modeling studies have been published. In one study, many individual models did not fit clinical data accurately, so the authors suggested that consolidating risk estimates from multiple models could yield more accurate predictions of toxicity risks.[266]

Summary and Other Key Points from QUANTEC Review[267]

The rectum is mobile and distensible, and therefore its position and volume can vary between and during radiation fractions. The superior and inferior borders of the rectum are not always easy to define on CT imaging. Most of the published studies of rectal toxicity address late rate rectal bleeding. However, most toxicity scoring systems are nonspecific, in that a patient can be considered as having a grade 2 or 3 event on the basis of diarrhea, stool frequency, rectal mucus, or bleeding. For patients undergoing radiation therapy for prostate cancer, it is recommended to limit the V50, V60, V65, V70, and V75 to less than 50%, 35%, 25%, 20%, and 15%, respectively. From a Phase I/II RTOG study published after the QUANTEC review,[268] in which 1009 men received 68.4 to 79.2 Gy, in 1.8 to 2.0 Gy fractions, rectal doses <60 Gy had no detectable impact on the fit of the NTCP model, and multivariate modeling showed only V75 to be significantly associated with late rectal toxicity.[269]

GASTROINTESTINAL SYSTEM: LIVER

Organ Function and Clinical Significance

The liver is a vital organ, with a breadth of metabolic functions including metabolism of ingested nutrients, detoxification, protein synthesis, bile production, glycogen storage, and red blood cell decomposition. Sequelae of radiation-induced liver damage include elevation of liver enzymes, ascites, jaundice, asterixis (tremor), encephalopathy, or coma. One of the most important patient-related predictors of susceptibility to liver damage is the baseline liver function, which is characterized by the Child-Pugh scoring system and accounts for serum bilirubin, albumin, coagulation times, the presence of ascites, and encephalopathy. The risk of radiation toxicity appears to be greater in the patient population with primary liver malignancies as opposed to liver metastases.

Dose-Volume Data

The RTOG 84-05 Phase I study, in which patients with liver metastases received whole liver radiation with 1.5 Gy twice daily fractions, none of the 122 patients who received 27 Gy to 30 Gy developed biochemical evidence of liver toxicity, compared to 5 of 51 who received 33 Gy.[270] In a study of 79 patients treated with liver radiotherapy at the University of Michigan, only those patients who received whole liver radiotherapy (1.5 to 1.65 Gy BID, with or without a boost) developed late radiation toxicity (crude risk of 9/33 versus 0/46 treated with partial liver radiation). Those who received a mean dose of >37 Gy (delivered twice daily with infusional fluorodeoxyuridine) and less sparing of normal liver had greater risk of late radiation toxicity (crude risk of 9/34 versus 0/45).[271]

Several studies have explored partial liver radiation in more detail, many of which used mean liver dose as a dose-volume metric. In a later study from University of Michigan, no late liver toxicity was observed with a mean liver dose <31 Gy, with NTCP models being optimized with a TD50 of 43 Gy and TD5 of 31 Gy for whole liver radiation; the risk of complications was strongly dependent on volume of liver irradiated.[272] Other risk factors for late toxicity included primary hepatobiliary carcinoma (as opposed to metastatic disease), use of bromodeoxyuridine chemotherapy (as opposed to fluorodeoxyuridine), and male gender. The NTCP models predict a TD5 in excess of 80 Gy if less than one third of the liver is irradiated. With irradiation of two thirds of the liver, the TD5 is on the order of 50 Gy and TD50 on the order of 60 Gy.

In a series from Taipei, patients with irradiated hepatocellular carcinoma who developed late liver toxicity had received a mean hepatic dose of 25 Gy (versus 20 Gy in patients without toxicity, $p = 0.02$).[273] The TD50 for whole liver, two thirds liver, and one third liver radiation were modeled to be approximately 43 Gy, 50 Gy, and 67 Gy, respectively. The TD5 for whole liver, two thirds liver, and one third liver radiation were modeled to be approximately 25 Gy, 28 Gy, and 38 Gy, respectively. The volume effect of liver radiation was less in this series. In another study from the same group, the mean liver dose and hepatitis B virus positivity were significant predictors or radiation toxicity; with NTCP modeling, the TD50 was ~50 Gy.[274]

In a Korean study of 105 patients with hepatocellular carcinoma, the mean dose and V20 to V40 parameters to total liver and normal liver (total liver minus GTV) were investigated.[275] The total liver V30 was the only significant parameter ($p < 0.001$). Grade ≥2 liver toxicity was observed in only 2.4% of patients with a total liver V30 ≤60% and 55% of patients with a total liver V30 >60% ($p < 0.001$). Another Korean study demonstrated a correlation of V15 with reduction in Child-Pugh score and recommends a V15 cutoff of <43.2%.[276]

The data from Asia differ from Western data, perhaps reflecting differences in the treated malignancy (mostly metastases in the West versus primary liver cancer in Asia, which often occurs in the setting of liver cirrhosis), radiation fractionation, and or concurrent therapies delivered with radiation.

Summary and Other Key Points from QUANTEC Review[277]

An understanding of radiation-induced liver toxicity necessitates an appreciation of liver motion. Extensive work has described liver motion as a result of breathing, which can displace the liver in excess of 2 cm. Preexisting liver dysfunction secondary to comorbid conditions such as hepatitis B or C infection and cirrhosis appears to increase the susceptibility to radiation-induced liver injury. For patients with liver metastases undergoing partial volume liver radiation, the risk of radiation induced liver toxicity appears to be more dependent upon the volume of liver irradiated. Partial volumes of liver can tolerate relatively high doses. Tolerances however

are lower for patients with primary liver cancer (who are more apt to have underlying liver disease). For whole liver radiation, doses ≤28 Gy to 30 Gy in 2 Gy fractions (28 Gy for liver metastases and 30 Gy for primary liver cancer) and ≤21 Gy in 3 Gy fractions are recommended. For partial liver radiation, treated with standard fractionation, the mean dose to normal liver (liver minus GTV) is suggested to be <30 Gy for liver metastases and <28 Gy for primary liver cancer.

GENITOURINARY SYSTEM: KIDNEY

Organ Function and Clinical Significance

The kidney functions to remove wastes, regulate electrolytes, produce erythropoietin, which stimulates red blood cell production, and modulate blood pressure through the renin-angiotensin pathway as well as through fluid/electrolyte balance. Perhaps late-kidney toxicity is underreported because of its long latency as well as toxicity being attributed to more common causes. Late renal complications include decreased kidney function, azotemia, hypertension, and kidney atrophy. Chronic radiation nephropathy in its mildest forms may not be diagnosed until years after therapy. Clinically silent abnormalities may include only proteinuria and azotemia with urinary casts and mild or no hypertension. Certainly, patients with only one functioning kidney or poor baseline renal function, are more vulnerable to damage (with or without symptoms) for any given volume of renal irradiation. Platinum and ifosfamide based chemotherapeutics can also impact renal function. Cisplatin at dosages greater than 200 mg/m^2 can result in glomerular or tubular injury and renal insufficiency.[278] Ifosfamide can cause glomerular and tubular toxicity, with renal tubular acidosis, or Fanconi syndrome. A study examining grades 3 to 4 ifosfamide-induced nephrotoxicity among adult and pediatric patients found a prevalence of 17% in both; neither age nor cumulative ifosfamide dose were risk factors.[279]

Dose-Volume Data

Several studies have investigated whole kidney dose tolerance, either after whole abdominal radiation or total body irradiation (generally delivered with lower fractional doses). Renal toxicity can occur after bilateral kidney doses ≥10 Gy, and the risk is quite high (50% to 80%) after 20 Gy. Thus, the kidneys have a relatively low threshold for damage. The dose volume-effect on the kidneys has been long recognized, even before the planning CT because kidneys are well visualized on plain simulation films. From these studies, when greater than half of the kidney receives doses >20 Gy to 30 Gy, or greater than one third receives >30 Gy to 40 Gy, patients are at increased risk of developing renal atrophy, decreased kidney function, and hypertension.[2,280-282]

There is little published on dose-volume parameters to predict late renal toxicity, in part because clinicians make an effort to minimize the volume of kidney exceeding the accepted tolerance dose. Low doses, 10 Gy to 15 Gy, to large volumes of kidney increase the risk of nephrotoxicity,[283-285] whereas smaller volumes of kidney exceeding ~20 Gy to 25 Gy can result in late renal toxicity.[283,285-287] In a series from Heidelberg, normal tissue complication modeling was used estimate the risk of late complications.[286] A median dose of ~17.5 Gy to 21.5 Gy and 22 Gy to 26 Gy corresponded to a 5% and 50% late complication risk (anemia, azotemia, hypertension, and edema), respectively. In another German study, reduced kidney function, as measured by scintigraphy changes, was analyzed as a function of dose and volume.[283] After irradiation of 10% to 30%, 30% to 60%, and 60% to 100% of the kidney volume to 20 Gy, the incidence of reduced activity was <10%, ~40%, and >70%, respectively. After irradiation of 10% to 30%, 30% to 60%, and 60% to 100% of the kidney volume to 30 Gy, the incidence of reduced activity was ~35%, >90%, and >98%, respectively. In a Dutch study of patients with gastric cancer (treated with concurrent radiation and cisplatin or capecitabine), the left kidney V20 ≥64% and mean left kidney dose of ≥30 Gy were associated with a significant decrease in left kidney function as compared to the right.[287] In a recent study of 125 patients with upper gastrointestinal malignancies, kidney V5 to V20 and mean kidney dose were significantly correlated with reduction in creatinine clearance.[288] A 15% to 20% decrease in creatinine clearance was associated with a V5 >50%, V10 >30%, V20 >30% (or >100 mL), and mean kidney dose >10 Gy.

Summary and Other Key Points from QUANTEC Review[289]

Radiation-associated kidney injury has a poorly understood pathophysiology and is likely underreported because of its long latency. For whole (bilateral) kidney radiation (not discussed), recommendations are for doses <10 Gy delivered over 5 to 6 fractions (at <6 cGy/min dose rate) and <15 to 18 Gy for radiation delivered over ≥5 weeks. For partial kidney radiation, the volume of kidneys receiving >20 Gy predicts risk of renal toxicity. The recommendation for partial kidney radiation is to maximally spare the kidneys and maintain a mean dose of <18 Gy to both kidneys or maintain a V6 <30% if one kidney cannot be adequately spared.

GENITOURINARY SYSTEM: BLADDER

Organ Function and Clinical Significance

The bladder is a highly distensible organ that collects urine. Symptoms from late radiation related toxicities include increased urinary frequency, hematuria, and dysuria. Necrosis, contracted bladder, and hemorrhage are less common, severe effects. Perhaps late-bladder toxicity is underreported because of its long latency as well as toxicity being attributed to more common causes. Because the bladder is mobile and distensible, determining accurate dose-volume (or dose-surface) constraints are challenging. Endpoints for bladder injury can reflect focal damage (e.g., bleeding) or more global injury (reduced bladder capacity with secondary urinary frequency). Recent data suggests that acute toxicity is predictive of late toxicity (particularly urinary frequency and hematuria) risks and pretreatment bladder dysfunction is predictive of late urinary symptoms (particularly urinary frequency, incontinence, and slow stream).[246]

Dose-Volume Data

Detailed dose-volume (or dose-surface) constraints have not been published, in part because of the complexities of assigning dose-volume metrics to a mobile, distensible structure. For whole bladder irradiation, doses in excess of 60 Gy, particularly with fraction sizes >2 Gy or accelerated radiation regimens, result in a significant risk of late grade ≥3 toxicity. Risks are lower when the whole bladder receives 45 Gy to 55 Gy, followed by a boost to >60 Gy to a portion of the bladder, though toxicity risk has not been correlated to dose-volume metrics. A recent Fox Chase Cancer Center study of 503 patients with prostate cancer examined urinary bladder V60 to V70 and area under the DVH, with bladder defined as just the bladder wall ("hollow" structure) or entire bladder and contents ("solid" structure); with multivariate analyses, the

mean bladder dose and area under the DVH were significant predictors of grade ≥2 genitourinary toxicity.[290] In a recent University of Chicago study of 296 patients with prostate cancer (in which the bladder was contoured as whole organ, after drainage and infusion of 120 mL of saline), no bladder dose-volume relationships were associated with the risk of grade ≥2 genitourinary toxicity.[263] With prostate cancer treated to high doses (≥72 Gy), the inferior portion of the bladder (e.g., trigone area) also receives ≥70 Gy. This tends to be well tolerated with respect to bladder toxicity. Arguably, the urinary toxicity that does develop after radiation results in part from the prostatic urethra receiving suprathreshold doses.

Summary and Other Key Points from QUANTEC Review[291]

The primary limitations of deriving strict dose-volume guidelines for the urinary bladder include the lack of robust 3D dose/volume data as well as the complicating factor that the bladder is a mobile structure of variable volumes/position. For whole bladder radiation, the reported risks of grade ≥3 toxicity in doses of 50 Gy to 60 Gy range from ≤5% to 40%. This variation is likely attributable to the challenges of correlating toxicity with dose delivered to a mobile structure, which is even more problematic when correlating partial volume exposures to toxicity. With the caveat of these issues, bladder constraints of ≤15%, ≤25%, ≤35%, and ≤50% receiving ≥80 Gy, ≥75 Gy, ≥70 Gy, and ≥65 Gy, respectively, as recommended in the RTOG 0415 study of prostate cancer, are suggested. The protocol advises an empty bladder at the time of simulation and treatment; the bladder is segmented from the base to the dome.

GENITOURINARY SYSTEM: PENILE BULB

Organ Function and Clinical Significance

The penile bulb is located at the base of the penis, caudal to the prostate.[292,293] Radiation dose to the penile bulb can affect erectile function, either as a direct result of damage to this structure (less likely) or damage to surrounding structures, whose radiation-induced damage is correlated with the dose exposure of the penile bulb. The most common scenario in which the penile bulb is irradiated is in the treatment of prostate cancer. IMRT is often used to minimize the dose to the penile bulb.[294,295] Interpretation of erectile dysfunction and the effect of penile bulb dose is complicated by preexisting function, comorbid conditions, and other therapies that may hinder (e.g., hormonal therapy) or help (e.g., drugs used to treat erectile dysfunction) erectile function. Also, determining which patients experience erectile dysfunction—a toxicity with varying severity—also complicates data interpretation.

Dose-Volume Data

Several studies have investigated dose-volume parameters to predict risk of erectile dysfunction. In several studies, no correlation was discerned for penile bulb dose and erectile function.[295-297] In one study, attempts were made to reduce the dose to the penile bulb (mean dose of 25 Gy), and thus few patients received high dose to the penile bulb.[295] In another study of 70 patients, no correlation was found for mean dose or maximal dose to the penile bulb, penile crura, or superiormost 1 cm of the penile crura; DVHs were also compared and found to be similar.[296]

In a small (21 patients), early study from University of California–San Francisco, patients receiving a D70 of <40%, 40% to 70%, and >70% to the penile bulb had a 0%, 80%, and 100% risk, respectively, of experiencing radiation-induced impotence.[298] In a study (29 patients) from Thomas Jefferson University, several dose-volume metrics were analyzed; a D30 >67 Gy, D45 >63 Gy, D60 >42 Gy, and D75 >20 Gy to the proximal penis were correlated with increased erectile dysfunction as well as ejaculatory function.[299] In a study from Royal Marsden Hospital, a D90 >50 Gy to the penile bulb was associated with significantly worse erectile function, whereas D15, D30, and D50 showed similar (albeit not significant) trend toward increased doses in impotent vs. intermediate potency versus potent patients.[300] Another recent small (19 patients) study found that mean dose <50 Gy was predictive of erectile potency.[301]

The largest study (158 patients) to date to investigate penile bulb dose is an analysis of the RTOG 9406 dose-escalation study.[302] A median dose of ≥52.5 Gy was associated with a greater risk of impotence (50% versus 25% at 5 years).

Summary and Other Key Points from QUANTEC Review[303]

There is some uncertainty regarding the critical anatomic structures for radiation-induced erectile dysfunction. Several studies from different academic centers have correlated the dose-volume exposure to the penile bulb with erectile dysfunction and have impressively similar results. Based on published data, it is recommended to keep the mean dose to 95% of the penile bulb <50 Gy and to limit the D70 and D90 to 70 Gy and 50 Gy, respectively.

CONCLUSIONS

The study of radiation-associated normal tissue injury has interested investigators for decades. Much progress has been made over the last 20 years. Additional technologies (e.g., gating, image-guided therapy) will provide some refinements in these physical advances. The emergence of novel technologies such as stereotactic body radiotherapy/stereotactic ablative body radiotherapy (SBRT/SABR), image-guided radiotherapy (IGRT), intensity-modulated radiotherapy (IMRT), charged particle therapy and four-dimensional planning have resulted in the increasing use of hypofractionated radiation, more conformal radiation delivery, and heterogeneous dose distributions (i.e., dose painting). Thus, future studies should account for fraction size and small-volume high-dose exposures. Eventually, models predicting dose/volume injury will likely more consistently consider the underlying physiology and substructures of organs, potential interactions between organs and differences in regional physiologic importance (e.g., different regions of the kidney being more important such as the cortex versus the medulla, different regions of the heart being more important, such as the coronary arteries or the left ventricle). There is a need to gain further understanding of the biological underpinnings of radiation-associated normal tissue damage. This will hopefully improve our abilities to predict, prevent, and treat radiation-associated normal tissue injury. As we employ more advanced technologies to further limit normal tissue exposure to lessen the risk of radiation-associated injury, we need to be careful not to compromise target coverage. Missing the tumor to avoid a grade 2 (or even grade 3 injury) might not be a reasonable trade-off, as a local tumor recurrence can be morbid. There are several published data sets that demonstrate that this is not a theoretical concern. In patients with orbital tumors and prostate cancer, more conformal techniques (applied to reduce normal tissue risks) have been associated with poorer clinical tumor control outcomes.[304,305] Radiation oncology is a dynamic field with constantly emerging technologic advances. In tandem with these advances is the critical

need for radiation oncologists to build their understanding of the normal tissue consequences of radiation administration. Not only do we need to explore associations of normal tissue damage with volume, dose, fraction size, and particle type, but we need to integrate this with the equally rapid evolution of novel systemic therapies and our pursuit of the pathophysiologic (including molecular genetics) basis of normal tissue injury.

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