Chapter 5

Physical and Radiobiological Evaluation of Radiotherapy Treatment Plan

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Additional information is available at the end of the chapter

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Abstract

Radiation treatment planning plays an important role in modern radiation therapy; it could simulate to plan the geometric, radiobiological, and dosimetric aspects of the therapy using radiation transport simulations and optimization. In this chapter, we have reviewed several quantitative methods used for evaluating radiation treatment plans and discussed some important considering points. For the purpose of quantitative plan evaluation, we reviewed dosimetrical indexes like PITV, CI, TCI, HI, MHI, CN, COSI, and QF. Furthermore, radiobiological indexes like Niemierko's EUD-based TCP and NTCP were included for the purpose of radiobiological outcome modeling. Additionally, we have reviewed dose tolerance for critical organs including RTOG clinical trial results, QUENTEC data, Emami data, and Milano clinical trial results. For the purpose of clinical evaluation of radiation-induced organ toxicity, we have reviewed RTOG and EORTC toxicity criteria. Several programs could help for the easy calculation and analysis of dosimetrical plan indexes and biological results. We have reviewed the recent trend in this field and proposed further clinical use of such programs. Along this line, we have proposed clinically optimized plan comparison protocols and indicated further directions of such studies.

Keywords: Treatment plan evaluation, Dosimetrical indices, Radiobiological indices, Tolerance doses, Radiation toxicity

1. Introduction

We have reviewed the methods used for quantitative comparison of different radiation treatment plans, the process of treatment plan comparison protocol, and the further direction of treatment plan evaluation programs. For the purpose of quantitative plan evaluation, we reviewed dosimetrical indexes like prescription isodose to target volume (PITV) ratio,

homogeneity index (HI), conformity index (CI), target coverage index (TCI), modified dose homogeneity index (MHI), conformity number (CN), critical organ scoring index (COSI), and quality factor (QF). Furthermore, radiobiological indexes like Niemierko's EUD-based tumor control probability (TCP) and normal tissue complication probability (NTCP) were included for the purpose of radiobiological outcome modeling. Additionally, we have reviewed dose tolerance for critical organs including RTOG clinical trial results, QUENTEC data, Emami data, and Milano clinical trial results. For the purpose of clinical evaluation of radiation-induced organ toxicity, we have reviewed RTOG and EORTC toxicity criteria. Several programs could help for the easy calculation and analysis of dosimetrical plan indexes and biological results. We have reviewed the recent trend in this field and proposed further clinical use of such programs. It is well known that plan comparison study still remain many controversies. The major issue is that plan evaluation methods are used in plan comparison and plan optimization. We have reviewed well-known dosimetric and biological plan indexes and several commercial and non-commercial plan evaluation programs. Along this line, we have proposed clinically optimized plan comparison protocols and indicated the further directions of such studies.

2. Background: Radiotherapy, radiation treatment planning, and planning decision support program

2.1. Radiotherapy

Over the past few decades, radiation treatment has become a technologically advanced field in modern medicine, especially with the advent of intensity-modulated radiation therapy (IMRT) [1]. Traditional radiation therapy planning is a manual, iterative, and simple process in which treatment fields are placed and beam modifiers are inserted.

Modifications are then made after manual inspection of the dose distribution calculated after each iteration [2]. In IMRT, the dose calculation engine specified dose distribution over the target volume and surrounding normal structures. Furthermore, dose calculation engine displayed a 2D dose intensity map by using its optimization algorithms [3]. Moreover, the inverse planning algorithm required users to set a dose/volume criteria for the specific organ/structure, and the computer calculated to find out a final solution to satisfy the criteria. [4]. Another breakthrough of modern radiation treatment is image-guided radiotherapy (IGRT). With the adoption and integration of imaging information in treatment designs, IGRT is the most innovative area in advanced radiotherapy [5]. IGRT has increased knowledge of exact tumor targets and their movements during the treatment process [6]. Despite improvements in target coverage and normal tissue sparing, the implementation of IMRT and IGRT remains a labor-intensive trial and error process. The creation of optimized treatment plans for personalized therapy still requires significant time and effort. Radiation treatment includes CT simulation, organ contouring, treatment planning, quality assurance, and dose delivery (Figure 1) [7].

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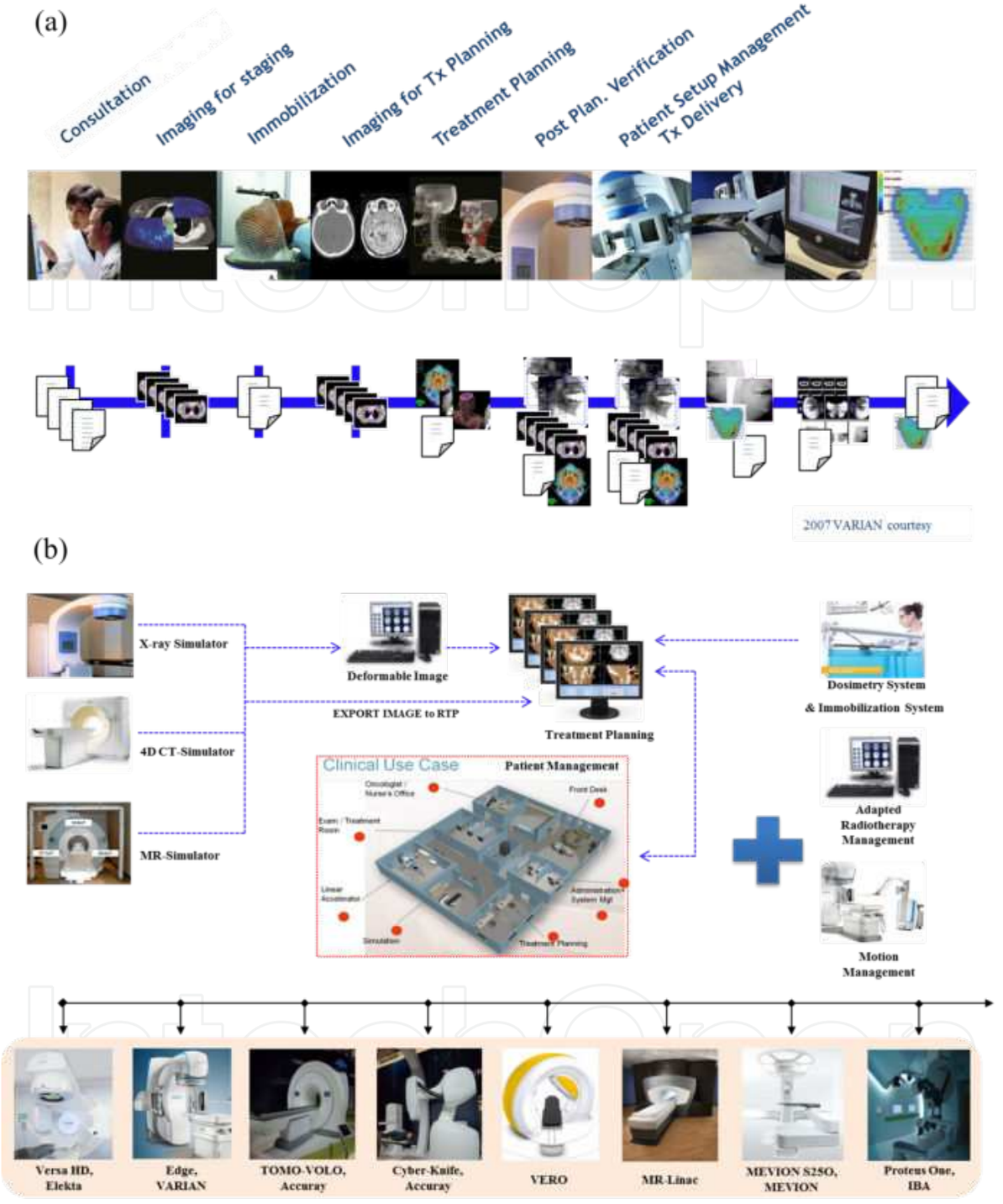

Figure 1. Clinical workflow of radiation treatment plan (a); radiation treatment includes CT simulation, organ contouring, treatment planning, quality assurance, and dose delivery. (b); configuration of radiotherapy equipment.

2.2. Radiation treatment planning

For radiation treatment, a team of radiation oncologists, radiation therapists, medical physicists, and medical dosimetrists plan the appropriate external beam radiotherapy treatment

technique for a patient with cancer [8]. There are generally two different types of planning algorithms, forward planning and inverse planning. The forward planning technique is mostly used in external-beam radiotherapy treatment planning process. For example, a medical physicist determines the beam angles in the treatment planning systems to maximize tumor dose when sparing the healthy tissues. This type of planning is used for the majority of external-beam radiotherapy treatments, but is only useful for relatively uncomplicated cases in which the tumor has a simple shape and is not near any critical organs. Inverse planning is a technique used to inversely design radiotherapy treatment plans (Figure 2). The radiation oncologist defines a patient's critical organs and tumor. Then, the dosimetrist provides target doses for each. An optimization program is then run to find the treatment plan that best matches all input criteria. This type of trial-and-error planning process is time and labor intensive.

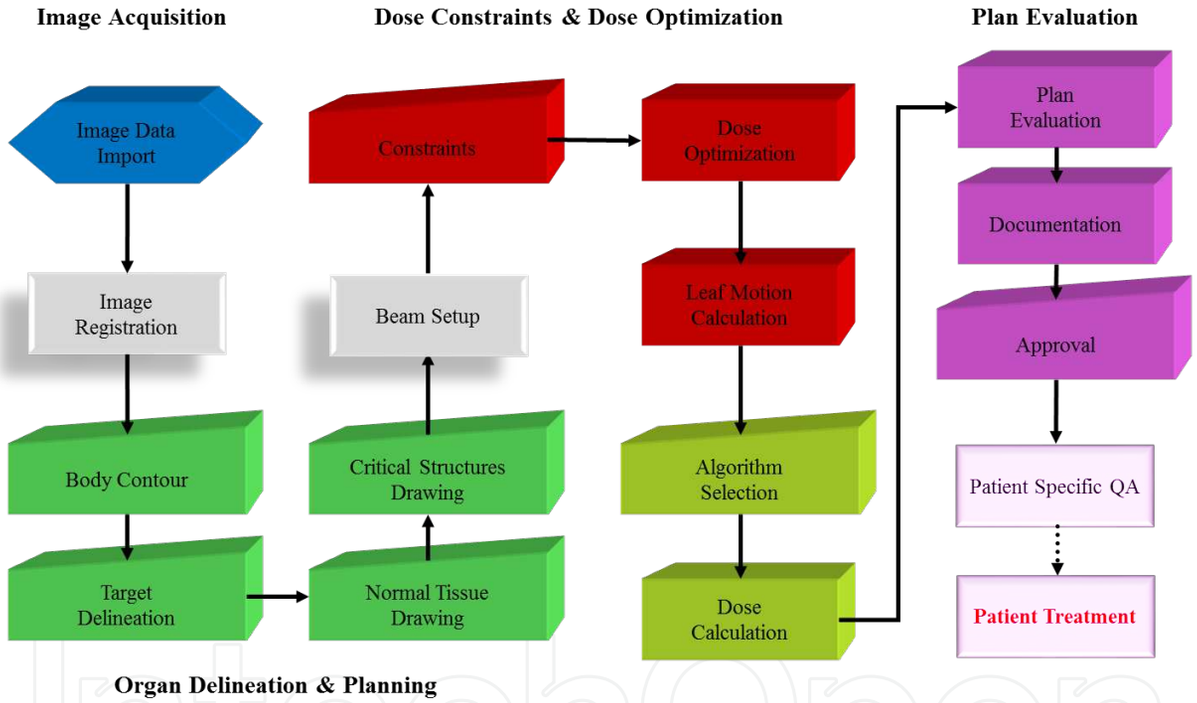

Figure 2. Workflow of inverse radiation treatment planning.

There are several commercial treatment planning systems (TPS) available nowadays. Table 1 summarizes information about commercial TPS [9].

2.3. Planning decision support program

Dose volume histogram (DVH) provides dose volume coverage information. However, it fails to provide more information like hot spot and dose homogeneity. Dosimetrical indices were widely used for plan evaluation for a specific purpose. For example, a homogeneity index refers to the intensity of dose distributions in target volume, those plans with both "hot" spot

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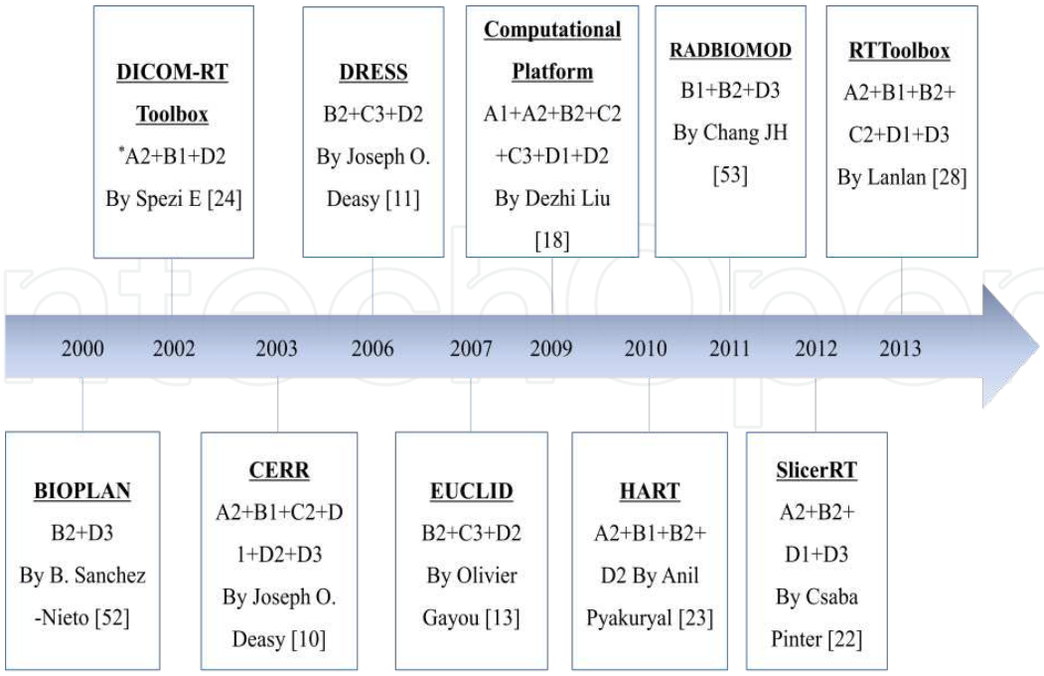
and "cold" spot could be distinguished by this index. Additionally, some indices consider dose conformity in the target volume. Conformity index was an example of such indices. Another method to review and evaluate treatment plan quality was biological index. A tumor control probability could indirectly estimate a tumor could be controlled by a certain dose. Furthermore, normal tissue complication probability could estimate the probability of a surrounding critical structure becomes some radiation-induced complications. Many programs have been designed and developed to calculate both dosimetrical and biological indices since the 2000s [10-29]. This is shown in Figure 3.

Treatment planning system	Company	Website
ScandiPlan	Scanditronix	http://www.scanditronix-magnet.se
Pinnacle3	Philips Healthcare	http://www.healthcare.philips.com
ISOgray	DOSIsoft	http://www.dosisoft.com
iPlan	Brainlab	https://www.brainlab.com
XiO	Electa	http://www.elekta.com
Monaco	Electa	http://www.elekta.com
Theraplan Plus	Electa	http://www.elekta.com
Oncentra MasterPlan	Electa	http://www.elekta.com
Oncentra Prostate	Electa	http://www.elekta.com
Oncentra GYN	Electa	http://www.elekta.com
Pinnacle	Philips Healthcare	http://www.healthcare.philips.com
Plato RTS	Electa	http://www.elekta.com
Plato BPS	Electa	http://www.elekta.com
Cad Plan	Varian Medical Systems	http://www.varian.com
Corvus	nomos	http://www.nomos.com
KL-Medical Electron Linear Accelerator treatment system	KLZ Healthcare	http://klz.comedb.com
Prowess 3-D	Prowess	http://www.prowess.com/
Brachyvision	Varian	http://www.varian.com
Leksell GammaPlan®	Electa	http://www.elekta.com
Eclipse	Varian Medical Systems	http://www.varian.com
VariSeed	Varian Medical Systems	http://www.varian.com
RayStation	RaySearch Laboratories	http://www.raysearchlabs.com

Table 1. Commercial RTP lists



*Legend		1	2	3
A	DICOM RT Platform	PACS compatible	3D Image module	-
B	Plan Comparison	Physical	Biological	Overall
C	Plan Analysis	Multi-RTP	Analysis DB	Statistical Analysis
D	Program	GUI Independence	Matlab	C, VB, Java, xls etc.

Figure 3. Timeline of plan analysis programs [10-11, 13, 17-18, 22-24, 28, 52-53].

3. Plan evaluation

3.1. Plan evaluation methods

3.1.1. Qualitative analysis

In conventional radiation therapy, an isodose distribution is used for plan analysis and evaluation. Figure 4 shows the typical isodose distribution of 3D conformal treatment plans and IMRT plans.

3.1.2. Quantitative analysis

DVH is the relationship between the dose distribution of a certain organ and 100% normalized volume of such organ. It was calculated and generated based on 3D reconstructed images in the treatment planning systems [9]. DVH could simplify 3D information of dose distribution

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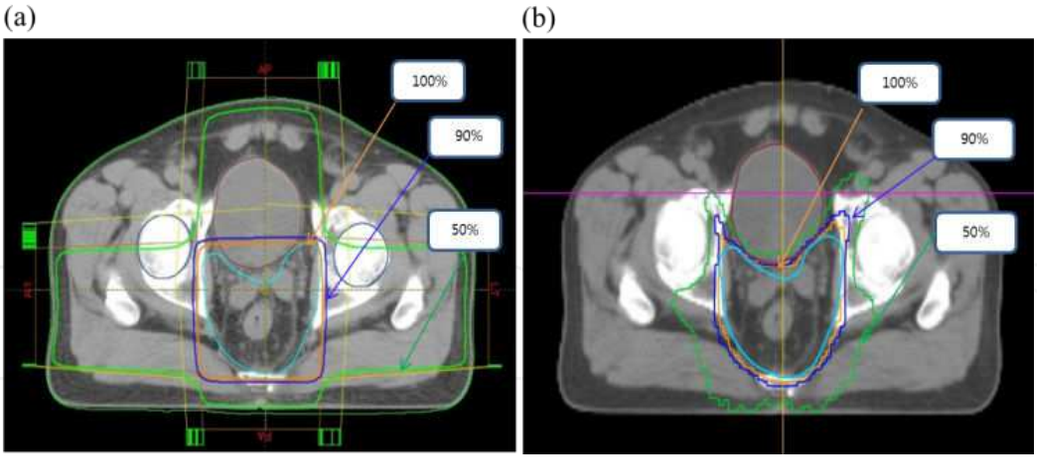

Figure 4. Typical isodose distribution of (a) 3D conformal treatment plan and (b) IMRT plan.

into a 2D graph or quantitative values [30-34]. Figure 5 shows a typical DVH for helical tomotherapy (HT) and intensity modulated proton therapy (IMPT) plans for prostate cancer.

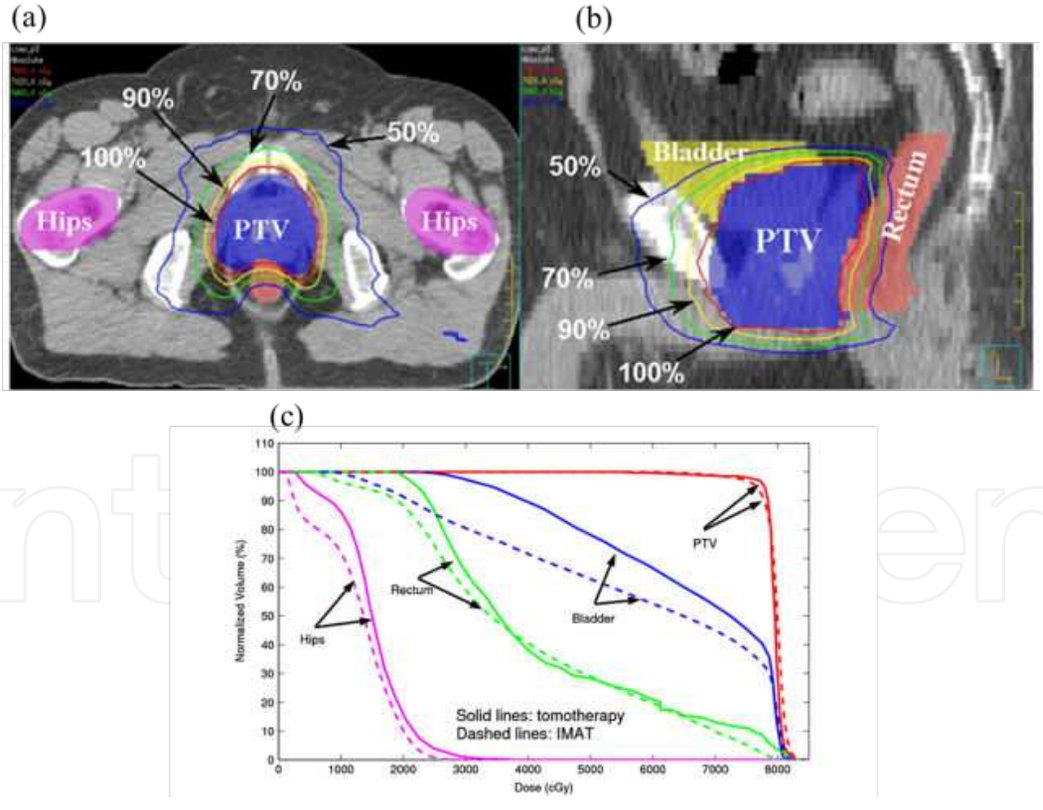

Figure 5. Typical DVH for helical tomotherapy (HT) treatment plan and intensity modulated arc therapy (IMAT) plan of prostate cancer: (a) axial slice, (b) sagittal slice. Planning target volume (PTV), critical structures, and four different isodose lines shown. (c) Dose-volume histogram comparison for prostate case. Solid lines, tomotherapy plan; dashed lines, intensity modulated arc therapy (IMAT) plan (International Journal of Radiation Oncology Biology Physics, 69(1), 2007).

4. Plan analysis

Isodose distribution and DVH analysis were insufficient compared to complicated and advanced planning techniques. As the femoral head DVHs in Figure 4 show, it was difficult to distinguish whether IMPT (continuous red line) or HT (dashed red line) plans were superior. For low dose volume (V_0 to V_{20}), IMPT was more favorable than HT. However, this relationship reversed for high dose volume (V_{20} to V_{50}). As a result, there are several indexes that may represent target conformity and dose homogeneity [31, 35-38].

4.1. Dosimetrical analysis

4.1.1. Index

Several quantitative evaluation tools were reviewed in this paper. These included the prescription isodose to target volume (PITV) ratio, homogeneity index (HI), conformity index (CI), target coverage index (TCI), modified dose homogeneity index (MHI), conformity number (CN), quality factor (QF) for PTV, maximum dose, mean dose, dose volume histogram (DVH), and critical organ scoring index (COSI) for the OAR (Figure 6).

4.1.2. PTV index

The PITV ratio, obtained by dividing prescription isodose surface volume by target volume, is expressed as:

$$PITV = \frac{PIV}{TV} \tag{1}$$

In the above equation, PIV represents prescription isodose surface volume and TV refers to target volume [39]. The PITV ratio is a conformity measure, and a value of 1.0 indicates that the volume of the prescription isodose surface equals that of the PTV. A PITV ratio of 1.0 does not necessarily imply that both volumes are similar. To ensure adequate PTV coverage, this measure should always be used in conjunction with a PTV-DVH [39]. The CI and HI indices for targets were computed to assess the quality of IMRT plans. CI is defined as the ratio of target volume and the volume inside the isodose surface that corresponds to the prescription dose. CI is generally used to indicate the portion of a prescription dose that is delivered inside the PTV [40].

CI is expressed as:

$$CI = \frac{PTV_{PD}}{PIV} \tag{2}$$

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In the above equation, PIV represents prescription isodose surface volume and PTV_{PD} represents PTV coverage at the prescription dose. CI of 1 indicates that 100% of a prescription dose is delivered to the PTV, and no dose is delivered to any adjacent tissue [40]. The CI is less than 1 for most clinical cases. Higher CI values indicate poorer dose conformity to the PTV. HI is defined as the ratio of maximum dose delivered to the PTV divided by the prescription dose delivered to the PTV [41].

HI is expressed as:

$$HI = \frac{D_{\max}}{PD} \tag{3}$$

In the above equation, D_{max} represents PTV maximum dose. An HI of 1 represents the ideal uniform dose within a target. Higher HI values indicate greater dose heterogeneity in the PTV [39].

TCI refers to the exact coverage of PTV in a treatment plan for a given prescription dose.

TCI is expressed as:

$$TCI = \frac{PTV_{PD}}{PTV} \tag{4}$$

In the above equation, PTV_{PD} represents PTV coverage at the prescription dose.

MHI is similar to HI, and is expressed as [41]:

$$MHI = \frac{D_{95}}{D_5} \tag{5}$$

In the above equation, D_{95} and D_5 represent doses received at 95% and 5% of the volume coverage, respectively.

Conformity number (CN) is a relative measurement of dosimetric target coverage and sparing of normal tissues in a treatment plan [42]. The CN is expressed as:

$$CN = TCI \times CI = \frac{PTV_{PD}}{PTV} \times \frac{PTV_{PD}}{PIV} \tag{6}$$

In the above equation, PTV_{PD} refers to PTV coverage at the prescription dose and PIV represents prescription isodose surface volume [42].

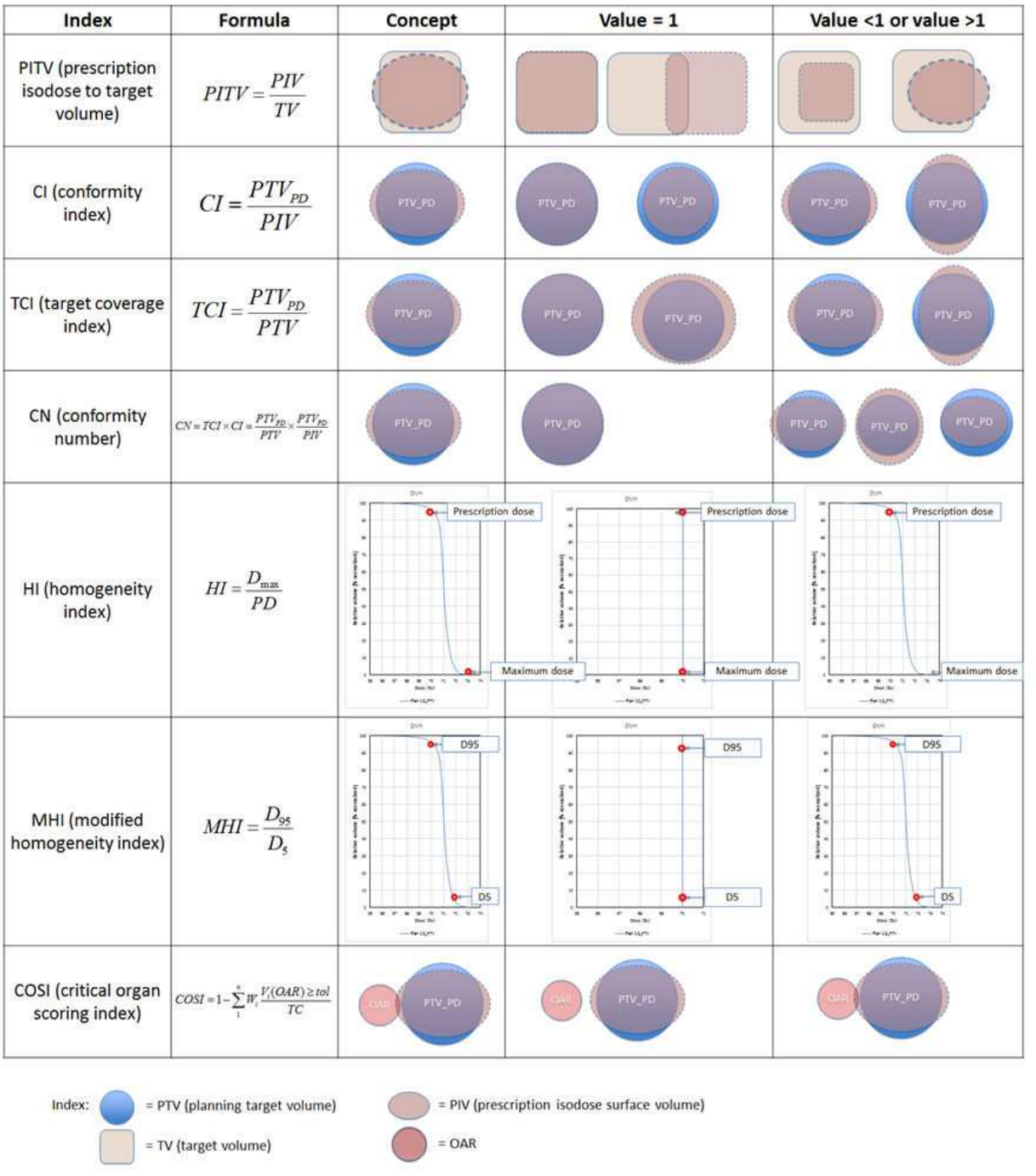

Figure 6. Comparison of the various dosimetrical indices in various clinical cases.

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4.2 Biological analysis

4.2.1. Overview of biological models

For radiobiological model-based plan evaluation, Niemierko's equivalent uniform dose (EUD)-based NTCP and TCP model were reviewed [12, 19]. First, the DVHs from each plan were exported from the appropriate treatment planning system (TPS) for each modality. The DVHs were then imported into MATLAB version R2012a (The Math Works, Inc., Natick, MA, USA) for TCP and NTCP modeling analysis. According to Neimierko's phenomenological model, EUD is defined as:

$$EUD = \left[\sum_{i=1} \left(V_i EQD_i^a \right) \right]^{\frac{1}{a}} \tag{7}$$

where *a* is a unitless model parameter that is specific to the nominal tumor structure of interest, and V_i is a unitless parameter that represents the i^{th} partial volume receiving dose D_i in Gy [12]. Since the relative volume of the whole structure of interest corresponds to 1, the sum of all partial volumes V_i will equal 1. In equation [5], the EQD is a biologically equivalent physical dose of 2 Gy defined as:

$$EQD = D \times \frac{\left(\frac{\alpha}{\beta} + \frac{D}{n_f} \right)}{\left(\frac{\alpha}{\beta} + 2 \right)} \tag{8}$$

where n_f and $d_f = D/n_f$ are the number of fractions and the dose per fraction size of the treatment course, respectively. In this equation, α/β is the tissue-specific linear quadratic (LQ) parameter of the organ being exposed. Niemierko's TCP [12] is defined as:

$$TCP = \frac{1}{1 + \left(\frac{TCD_{50}}{EUD} \right)^{\gamma 50}} \tag{9}$$

where TCD_{50} is the tumor dose required to control 50% of cancer cells when a tumor is homogeneously irradiated and γ_{50} is a unitless model parameter that is specific to the tumor of interest. The slope of the dose response curve is described by γ_{50}. Niemierko's NTCP [19] is defined as:

$$TCP = \frac{1}{1 + \left(\frac{TCD_{50}}{EUD} \right)^{\gamma 50}} \tag{10}$$

where TD_{50} is the tolerance dose of a 50% complication rate at a specific time (e.g. 5 years in the Emami et al. normal tissue tolerance data [43]) for an entire organ of interest. This parameter also describes the slope of the dose response curve.

4.3. Overall plan index

4.3.1. Overall plan index

A comprehensive quality index (CQI) including surrounding OARs were introduced to evaluate the individual difference between OARs and PTV and the small volume of critical structures. CQI is expressed as [44]:

$$CQI = \frac{1}{N}\sum_{i=1}^{N} QI_i = \frac{1}{N}\sum_{i=1}^{N} \frac{\left(D_{\max}^{plan1}\right)}{\left(D_{\max}^{plan2}\right)} \tag{11}$$

In this equation, I is the index of the critical organs, which are several critical structures in certain plan. CQI was designed to compare the ability of avoiding these organs around the PTV given the same weighting to all organs. Although CQI may overweight certain organs that are below tolerance, we chose this index as it represents a global measure of the capability of avoiding sensitive structures. Individual Qis are shown for direct comparison of each OAR. A CQI less than one indicates that HT provides a better plan for the surrounding OARs, and vice versa.

4.3.2. COSI

The COSI index accounts for both target coverage and critical organ irradiation [45]. The main advantage of this index is its ability to distinguish between different critical organs. COSI is expressed as:

$$COSI = 1 - \sum_{1}^{n} w_i \frac{V_i\left(OAR\right)_{>tol}}{TCI} \tag{12}$$

where $V_i(OAR)_{>tol}$ is the volume fraction of OAR that receives more than a predefined tolerance dose. TCV is the volumetric target coverage, which is defined as the fractional volume of PTV covered by the prescribed isodose. Modified COSI is expressed as:

$$mCOSI = \sum_{i=1} W_i \left(\frac{COSI_{10} + COSI_{20} + \cdots + COSI_{80}}{8} \right) \tag{13}$$

Although the COSI index focuses only on OARs that receive high dose region volumes, the modified COSI considers both high dose and low dose regions.

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4.3.3. Quality factor

The quality factor (QF) introduced in this study is a dosimetrical index that can evaluate the quality of an entire plan [23]. The QF of a plan is analytically expressed as:

$$QF = \left[2.718 \exp\left(-\sum_{i=1}^{N} W_i X_i \right) \right] \tag{14}$$

In the above equation, X_i represents all PTV indices, including PITV, CI, HI, TCI, MHI, CN, and COSI. The weighting factor (W_i) values can be adjusted between 0 and 1 for all relatively weighted indices for a user-defined number of indices (N). A weighting factor of 1 was used for all separate indices. Thus, the QF was mainly used to compare the conformity of plans throughout various trials of a treatment.

5. Radiation tolerance dose and toxicity

The dose to critical structures plays an important role in treatment plan evaluation and is a challenging parameter in radiotherapy treatment planning. Here, Emami data [43], QUENTEC data [46], RTOG data, and the Milano study were reviewed. Doses based on tumor location in the body related to critical organs are as follows (Table 2-4).

5.1. Radiation toxicities

The assessment and reporting of toxicity plays a central role in oncology [47-50]. The foundation of toxicity reporting is the toxicity criteria system. Multiple systems have been developed in the last 30 years, and they have evolved substantially since their first introduction. The wide adoption of standardized criteria will facilitate comparison between institutions and clinical trials.

The Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring criteria developed in 1984 consists of 13 scales that cover most body regions [51]. This system was used by the RTOG and in other clinical trials for over 30 years. The inclusion of acute radiation criteria into a multimodality grading system facilitated toxicity grading in all oncologic disciplines. This system also allows radiation oncologists to recognize and grade toxicities that were not available in the previous RTOG system. Tables 5 and 6 summarize acute toxicity categorized by body region.

The RTOG/EORTC (European Organization for Research and Treatment of Cancer) system for scoring late effects was developed in 1984 alongside the RTOG acute criteria. It contains 16 organ categories (Tables 7, 8) and has been used widely. However, its shortcomings have prompted the development of other systems.

RTOG data							QUANTEC data						Emami Data							Milano Data		
Critical Structure	**Dose/ fx**	**Vol.**	**Dose**	**Max. Dose**	**Protocol**	**Treated organ**	**Critical Structure**	**Vol.**	**Dose/ Vol.**	**Max. Dose**	**Toxicity Rate**	**Toxicity Endpoint**	**Organ**	**TD 5/5**	**TD 50/5**					**Organ**	**Dose tolerance**	**Endpoint**
Brachial Plexus	2 Gy	5%	60 Gy		619	Postop H&N	Brain			<60 Gy	<3%	Symptomatic necrosis		Whole	2/3	1/3	Whole	2/3	1/3			
	2 Gy			60 Gy	522	Definitive H&N				72 Gy	5%	Symptomatic necrosis	Brain	4500	5000	6000	6000	6500	7500			
	2 Gy			66 Gy	0619, 0617	Postop H&N, lung, nasopharynx				90 Gy	10%	Symptomatic necrosis										
	3 Gy			36 Gy	937	Lung							Brachial plexus	6000	6100	6200	7500	7600	7700			
	4 Gy			30 Gy	937	Lung																
Brainstem	1.8-2Gy	0.03cc		55 Gy (0.03 cc)	539	Intermediate risk meningioma	Brain stem			<54 Gy	<5%	Neuropathy or necrosis	Brain stem	5000	5300	6000	6500	–	–	Brain stem	V60 < 0.9 mL	<5% grade >= 1 toxicity
	33 fxs			54 Gy	615	Nasopharynx		D1-10 cc	<= 59 Gy		<5%	Neuropathy or necrosis										
	1.8-2Gy			60 Gy (0.03 cc)	0539, 0825	High risk meningioma, glioblastoma				<64 Gy	<5%	Neuropathy or necrosis										
	2 Gy			52 Gy (0.03 cc	1016	Oropharynx																
Cochlea	33 fxs	5%	55 Gy		615	Nasopharynx	Cochlea	Mean	<=45 Gy		<30%	Sensory-neural hearing loss	Ear	5500	5500	5500	6500	6500	6500			
Larynx, glottis	Mean	20 Gy			1016	Oropharynx	Larynx			<66 Gy	<20%	Vocal dysfunction	Larynx (necrosis)	7000	7000	7900	8000	8000	9000			
	2 Gy			45 Gy	0619, 0615	Postop H&N, definitive H&N, nasopharynx		Mean	<50 Gy		<30%	Aspiration	Larynx (edema)	4500	4500	–	8000	–	–			
								Mean	<44 Gy		<20%	Edema										
								V50	<27%		<20%	Edema										

RTOG data							QUANTEC data						Emami Data								Milano Data		
Critical Structure	Dose/ fx	Vol.	Dose	Max. Dose	Protocol	Treated organ	Critical Structure	Vol.	Dose/ Vol.	Max. Dose	Toxicity Rate	Toxicity Endpoint	Organ	TD 5/5			TD 50/5				Organ	Dose tolerance	Endpoint
Lens	1.8-2Gy			5 Gy (0.03 cc)	539	Intermediate risk meningioma							Lens	1000	–	–	1800	–	–				
	1.8-2Gy			7 Gy (0.03 cc)	0539, 0825	High risk meningioma, glioblastoma																	
	33 fxs			25 Gy	615	Nasopharynx																	
Lips	2 Gy	Mean	<20 Gy		1016	Oropharynx																	
Mandible/ TM joint	2 Gy			66 Gy	1016	Oropharynx																	
	33 fxs	1 cc	75 Gy		615	Nasopharynx							TMJ mandi-ble	6000	6000	6500	7200	7200	7700				
	33 fxs			50 Gy	615	Nasopharynx																	
Optic chiasm	33 fxs			50 Gy	615	Nasopharynx	Optic nerve/ chiasm			<55 Gy	<3%	Optic neuropathy	Optic chiasm	5000	–	–	6500	–	–				
	1.8-2 Gy			54 Gy (0.03 cc)	539	Intermediate risk meningioma				55-60 Gy	3-7%	Optic neuropathy											
	1.8-2 Gy			56 Gy (0.03 cc)	0539, 0825	High risk meningioma, glioblastoma				>60 Gy	>7-20%	Optic neuropathy											
Optic nerve	1.8-2 Gy			50 Gy (0.03 cc)	0539, 0615	Intermediate risk meningioma, nasopharynx																	
	1.8-2 Gy			55 Gy (0.03 cc)	0539, 0825	High risk meningioma, glioblastoma							Optic nerve	5000	–	–	6500	–	–				
Oral cavity	33 fxs	Mean	<40 Gy		615	Nasopharynx																	
Oral cavity (non-involved)	2 Gy	Mean	<30 Gy	60 Gy	1016	Oropharynx																	

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Table 2. Radiation tolerance dose in head and neck

RTOG data							QUANTEC data						Emami Data							Milano Data		
Critical Structure	**Dose/ fx**	**Vol.**	**Dose**	**Max. Dose**	**Protocol**	**Treated organ**	**Critical Structure**	**Vol.**	**Dose/ Vol.**	**Max. Dose**	**Toxicity Rate**	**Toxicity Endpoint**	**Organ**	**TD 5/5**			**TD 50/5**			**Organ**	**Dose tolerance**	**Endpoint**
Parotid Glands	2 Gy	Mean one gland	<26 Gy		0619, 0522, 1016	Postop H&N, definitive H&N, oropharynx	Parotid, bilateral	Mean	<=25 Gy		<20%	Long-term salivary function <25%										
	2 Gy	V50 one gland	<30 Gy		0619, 0522	Postop H&N, definitive H&N		Mean	<=39 Gy		<50%	Long-term salivary function <25%	Parotid gland	3200	3200	–	4600	4600		Parotid	Mean dose < 26 Gy	Late grade 2 xerostomia, >75% functional loss
	2 Gy	Combined 20 cc	<20 Gy		0619, 0522	Postop H&N, definitive H&N	Parotid, unilateral	Mean	<=20 Gy		<20%	Long-term salivary function <25%										
Pharynx, postcricoid	33 fxs			45 Gy	615	Nasopharynx																
Pharynx, posterior wall	2 Gy	33%	50Gy		1016	Oropharynx	Pharyngeal constrictors	Mean	<=50 Gy		<20%	Symptomatic dysphagia and aspiration										
	2 Gy	15%	60Gy		1016	Oropharynx																
	2 Gy	Mean	45Gy		1016	Oropharynx																
Retina	1.8-2 Gy			45 Gy (0.03 cc)	539	Intermediate risk meningioma																
	1.8-2 Gy			50 Gy (0.03 cc)	0539, 0825, 0615	High risk meningioma, glioblastoma, nasopharynx							Retina	4500	–	–	6500	–	–			
Spinal Cord	1.8 Gy			45 Gy	0623, 0615	Lung, Nasopharynx				50 Gy	0.20%	Myelopathy	Spinal cord	(20cm)	(10cm)	(5 cm)	–	(10cm)	(5 cm)	Spinal cord	Max < 50 Gy	<5% grade >= 3 toxicity
	2 Gy			48 Gy (0.03 cc)	0619, 0522	Postop H&N, definitive H&N	Spinal cord			60 Gy	6%	Myelopathy		4700	5000	5000		7000	7000	Cervical spinal cord	EUD < 52 Gy, Max < 55 Gy	<5% grade >= 3 toxicity
Submandibular Gland	2 Gy	Mean	<39 Gy		1016	Oropharynx				69 Gy	50%	Myelopathy										

RTOG data							QUANTEC data							Emami Data							Milano Data		
Critical Structure	**Dose/ fx**	**Vol.**	**Dose**	**Max. Dose**	**Protocol**	**Treated organ**	**Critical Structure**	**Vol.**	**Dose/Vol.**	**Max. Dose**	**Toxicity Rate**	**Toxicity Endpoint**	**Organ**	**TD 5/5**	**TD 50/5**					**Organ**	**Dose tolerance**	**Endpoint**
Esophagus	1.8 Gy	Mean	34 Gy		0623, 0617	Lung	Esophagus	Mean	<34 Gy		5-20%	Grade 3+ esophagitis	Esophagus	Whole	2/3	1/3	Whole	2/3	1/3	Esophagus	V50 and S50 < 30%	5% risk of late toxicity
	1.8 Gy	10 cm	60 Gy		623	Lung		V35	<50%		<30%	Grade 2+ esophagitis		5500	5800	6000	6800	7000	7200			
	2 Gy	Mean	30 Gy		1016	Oropharynx		V50	<40%		<30%	Grade 2+ esophagitis	(stricture, perforation)									
	3 Gy			47 Gy	937	Lung		V70	<20%		<30%	Grade 2+ esophagitis	Thyroid	4500			8000					
Heart	1.8 Gy	33%	60 Gy		0623, 0617	Lung	Heart ,Pericardium	Mean	<26 Gy		<15%	Pericarditis	Heart	4000	4500	6000	5000	5500	7000	Heart	V33 < 60%	5% excess cardiac mortality
	1.8 Gy	33%	50 Gy		436	Esophagus		V30	<46%		<15%	Pericarditis	(pericarditis)								V38 < 33%	
	1.8 Gy	67%	45 Gy		0623, 0617 0436	Lung, esophagus	Heart	V25	<10%		<1%	Long term cardiac mortality									V42 < 20%	
	1.8 Gy	100%	40 Gy		0623, 0617 0436	Lung, esophagus																
	3 Gy			47 Gy	937	Lung																
	3 Gy	V45	<30%		937	Lung																

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RTOG data							QUANTEC data						Emami Data							Milano Data		
Critical Structure	**Dose/ fx**	**Vol.**	**Dose**	**Max. Dose**	**Protocol**	**Treated organ**	**Critical Structure**	**Vol.**	**Dose/Vol.**	**Max. Dose**	**Toxicity Rate**	**Toxicity Endpoint**	**Organ**	**TD 5/5**		**TD 50/5**				**Organ**	**Dose tolerance**	**Endpoint**
Lung, single	2 Gy	3 cm CW to field			413	Breast		V20	<=30%		<20%	Symptomatic pneumonitis	Lung	1750	3000	4500	2450	4000	6500		V13 < 40%	Late grade 2 in <10-20%
	2 Gy	V20	20%		630	Sarcoma		Mean	7 Gy		5%	Symptomatic pneumonitis	Rib cage	–	–	5000	–	–	6500		V20 < 25-30%	Late grade 3 in <5-10%
	2 Gy	V20	37%		0617, 0623	Lung		Mean	13 Gy		10%	Symptomatic pneumonitis								Lung	V30 < 10-15%	
Lungs, total	2 Gy	Mean	20 Gy		617	Lung	Lung	Mean	20 Gy		20%	Symptomatic pneumonitis									MLD < 10-20 Gy	
	3 Gy	Mean	20 Gy		937	Lung		Mean	24 Gy		30%	Symptomatic pneumonitis										
	3 Gy	V20	<= 30%		937	Lung		Mean	27 Gy		40%	Symptomatic pneumonitis										
Small Bowel	3 Gy	150 cc	30 Gy		937	Lung	Small bowel (individual loops)	V15	<120 cc		<10%	Grade 3+ toxicity	Small intestine (obstruction, perforation)	4000	–	5000	5500	–	6000			
	3 Gy	100 cc	35 Gy		937	Lung	Small bowel (peritoneal cavity)	V45	<195 cc		<10%	Grade 3+ toxicity										
	3 Gy	50 cc	40 Gy		937	Lung																
	3 Gy	1 cc	45 Gy		937	Lung																
	4 Gy	100 cc	30 Gy		937	Lung																
	4 Gy	50 cc	35 Gy		937	Lung							Stomach (ulceration,perforation)	5000	5500	6000	6500	6700	7000			
	4 Gy	1 cc	40 Gy		937	Lung	Stomach	D100	<45 Gy		<7%	Ulceration										

RTOG data							QUANTEC data						Emami Data								Milano Data		
Critical Structure	**Dose/ fx**	**Vol.**	**Dose**	**Max. Dose**	**Protocol**	**Treated organ**	**Critical Structure**	**Vol.**	**Dose/Vol.**	**Max. Dose**	**Toxicity Rate**	**Toxicity Endpoint**	**Organ**	**TD 5/5**			**TD 50/5**				**Organ**	**Dose tolerance**	**Endpoint**
Spinal Cord	1.8 Gy			45 Gy	0623, 0615	Lung, Nasopharynx	Spinal cord			50 Gy	0.20%	Myelopathy	Spinal cord	(20 cm)	(10 cm)	(5 cm)	–	(10 cm)	(5 cm)		Spinal cord	Max < 50 Gy	<5% grade >= 3 toxicity
	2 Gy			50.5	617	Lung				60 Gy	6%	Myelopathy		4700	5000	5000		7000	7000		Cervical spinal cord	EUD < 52 Gy	<5% grade >= 3 toxicity
	1.8 Gy	10 cm	50 Gy		436	Esophagus				69 Gy	50%	Myelopathy										Max < 55 Gy	
	1.8 Gy	20 cm	47 Gy		436	Esophagus																	
	3 Gy			36 Gy	937	Lung																	
	4 Gy			30 Gy	937	Lung																	
Kidney	1.8 Gy	100%	23 Gy		436	Esophagus	Kidney, bilateral	Mean	<15-18 Gy		<5%	Clinical dysfunction	Kidney	2300	3000	5000	2800	4000	–		Kidney	Median dose < 17.5 Gy	Anemia,, azotemia, HTN, edema
	1.8 Gy	67%	30 Gy		436	Esophagus		Mean	<28 Gy		<50%	Clinical dysfunction											
	1.8 Gy	33%	50 Gy		436	Esophagus		V12	<55%		<5%	Clinical dysfunction											
	2 Gy	50%	14 Gy		630	Sarcoma		V20	<32%		<5%	Clinical dysfunction											
	3 Gy	V18	< 25%		937	Lung		V23	<30%		<5%	Clinical dysfunction											

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Table 3. Radiation tolerance dose in abdomen

RTOG data							QUANTEC data						Emami Data							Milano Data		
Critical Structure	**Dose/ fx**	**Vol.**	**Dose**	**Max. Dose**	**Protocol**	**Treated organ**	**Critical Structure**	**Vol.**	**Dose/Vol.**	**Max. Dose**	**Toxicity Rate**	**Toxicity Endpoint**	**Organ**	**TD 5/5**	**TD 50/5**					**Organ**	**Dose tolerance**	**Endpoint**
Liver	1.8 Gy	50%	35 Gy		436	Esophagus	Liver	Mean	<30-32 Gy		<5%	RILD (in normal liver function)	Liver	3000	3500	5000	4000	4500	5500	Liver	1/3: 40-80 Gy	Late grade 3-4 liver toxicity < 5%
	3 Gy	>700 cc	<18 Gy		937	Lung		Mean	<42 Gy		<50%	RILD (in normal liver function)									2/3: 30-50 Gy	
								Mean	<28 Gy		<5%	RILD (in Child-Pugh A or HCC)									3/3: 25-35%	
								Mean	<36 Gy		<50%	RILD (in Child-Pugh A or HCC)										

	RTOG data						Handbook			QUANTEC data					Emami Data							Milano Data		
Critical Structure	**Dose/fx**	**Vol.**	**Dose**	**Max. Dose**	**Protocol**	**Treated organ**	**Organ**	**Partial Organ**	**Tolerance (1.8 – 2.0 Gy/fx)**	**Critical Structure**	**Vol.**	**Dose/ Vol.**	**Max. Dose**	**Toxicity Rate**	**Toxicity Endpoint**	**Organ**	**TD 5/5**	**TD 50/5**				**Organ**	**Dose tolerance**	**End point**
	1.8 Gy	60%	50 Gy		621	Prostate		Whole	50 Gy (5-10% late)	Bladder (bladder cancer)			<65	<6%	Grade 3+ toxicity		Whole	2/3	1/3	Whole	2/3	1/3			
	1.8 Gy	60%	40 Gy		534	Postop prostate		Whole	60 Gy (10-40% late)		V65	<50%			Grade 3+ toxicity	Bladder	6500	8000	N/A	8000	8500	N/A			
	1.8 Gy	55%	50 Gy		PMID 18947938	RTOG Prostate Group Consensus 2009	Bladder	1/3	60 Gy (5-10% late)	Bladder (prostate cancer)	V70	<35%			Grade 3+ toxicity										
	1.8 Gy	50%	35 Gy		529	Anus		1/3	70 Gy (20% late)		V75	<25%			Grade 3+ toxicity										
	1.8 Gy	50%	65 Gy		415	Prostate		GYN HDR	<70% Point A		V80	<15%			Grade 3+ toxicity										
	1.8 Gy	40%	40 Gy		822	Rectum	Urethra		60-70 Gy																
	1.8 Gy	40%	65 Gy		534	Postop prostate	Testis	Transient azospermia	0.5 Gy																
Bladder	1.8 Gy	40%	66.6 Gy		621	Prostate		Total azospermia	0.8-1 Gy																
	1.8 Gy	35%	40 Gy		529	Anus		Sterilization	2-3 Gy																
	1.8 Gy	35%	45 Gy		418	Endometrial	Ovary	Sterilization	2-3 Gy																
	1.8 Gy	35%	70 Gy		415	Prostate		Ovarian failure	5-10 Gy																
	1.8 Gy	30%	70 Gy		PMID 18947938	RTOG Prostate Group Consensus 2009	Vagina	Upper mucosa	120 Gy																
	1.8 Gy	25%	75 Gy		415	Prostate		Mid mucosa	80-90 Gy																
	1.8 Gy	15%	45 Gy		822	Rectum		Lower mucosa	60-70 Gy																
	1.8 Gy	15%	80 Gy		415	Prostate		Fibrosis/stenosis	>50-60 Gy																
	1.8 Gy	5%	50 Gy		529	Anus	Ureter		<75 Gy																
	1.8 Gy			50 Gy	822	Rectum																			

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RTOG data							Handbook			QUANTEC data						Emami Data						Milano Data		
Critical Structure	**Dose/fx**	**Vol.**	**Dose**	**Max. Dose**	**Protocol**	**Treated organ**	**Organ**	**Partial Organ**	**Tolerance (1.8 – 2.0 Gy/fx)**	**Critical Structure**	**Vol.**	**Dose/ Vol.**	**Max. Dose**	**Toxicity Rate**	**Toxicity Endpoint**	**Organ**	**TD 5/5**		**TD 50/5**			**Organ**	**Dose tolerance**	**End point**
External genitalia	1.8 Gy	50%	20 Gy		529	Anus																		
	1.8 Gy	35%	30 Gy		529	Anus																		
	1.8 Gy	5%	40 Gy		529	Anus																		
Femoral Head	1.8 Gy	50%	30 Gy		529	Anus	Femoral head	Adult	42-50 Gy															
	1.8 Gy	15%	30 Gy		418	Endometrial		Slipped epiphysis	<25 Gy															
	1.8 Gy	40%	40 Gy		822	Rectum		Avascular necrosis	30-40 Gy															
	1.8 Gy	35%	40 Gy		529	Anus																		
	1.8 Gy	25%	45 Gy		822	Rectum																		
	1.8 Gy	10%	50 Gy		534	Postop prostate																		
	1.8 Gy	5%	44 Gy		529	Anus																		
	1.8 Gy	5%	50 Gy		PMID 18947938	RTOG Prostate Group Consensus 2009																		
	2 Gy	5%	60 Gy		630	Sarcoma																		
	1.8 Gy			50 Gy	822	Rectum																		
	1.8 Gy			45 Gy	712	Bladder																		
Iliac crests	1.8 Gy	50%	30 Gy		529	Anus																		
	1.8 Gy	35%	40 Gy		529	Anus																		
	1.8 Gy	5%	50 Gy		529	Anus																		
Large Bowel	1.8 Gy	50%	35 Gy		529	Anus										Colon	4500	–	5500	5500	–	6500			
	1.8 Gy	35%	40 Gy		529	Anus				Penile bulb	Mean dose to 95% gland	<50 Gy		<35%	Severe erectile dysfunction	obstruction, perforation, ulceration								
	1.8 Gy	5%	50 Gy		529	Anus					D90	<50 Gy		<35%	Severe erectile dysfunction									
Penile Bulb	1.8 Gy	Mean	52.5 Gy		415	Prostate					D60-70	<70 Gy		<55%	Severe erectile dysfunction									

RTOG data							Handbook			QUANTEC data							Emami Data						Milano Data		
Critical Structure	Dose/fx	Vol.	Dose	Max. Dose	Protocol	Treated organ	Organ	Partial Organ	Tolerance (1.8 – 2.0 Gy/fx)	Critical Structure	Vol.	Dose/ Vol.	Max. Dose	Toxicity Rate	Toxicity Endpoint	Organ	TD 5/5			TD 50/5			Organ	Dose tolerance	End point
Rectum	1.8 Gy	60%	30 Gy		418	Endometrial	Rectum	Whole	60 Gy	Rectum	V50	<50%		<10%	Grade 3+ toxicity	Rectum severe proctitis, necrosis, fistula, stenosis	6000	–	–	8000	–	–	Rectum	V70-80 <= 15 cc V70 <= 20-25%	Late grade 2 in < 5-10%
	1.8-2 Gy	50%	55 Gy		712	Bladder		GYN HDR	<70% Point A		V60	<35%		<10%	Grade 3+ toxicity										
	1.8 Gy	50%	50 Gy		0621, PM ID 18947938	Prostate					V65	<25%		<10%	Grade 3+ toxicity										
	1.8 Gy	50%	60 Gy		415	Prostate					V70	<20%		<10%	Grade 3+ toxicity										
	1.8 Gy	35%	65 Gy		415	Prostate					V75	<15%		<10%	Grade 3+ toxicity										
	1.8 Gy	25%	66.6 Gy		621	Prostate																			
	1.8 Gy	25%	70 Gy		415	Prostate																			
	1.8 Gy	15%	75 Gy		415	Prostate																			
	1.8 Gy	45%	40 Gy		534	Postop prostate																			
	1.8 Gy	25%	65 Gy		534	Postop prostate																			
	1.8 Gy	20%	70 Gy		PMID 18947938	RTOG Prostate Group Consensus 2009																			

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Table 4. Radiation tolerance dose in pelvis

	RTOG data						Handbook			QUANTEC data						Emami Data						Milano Data		
Critical Structure	**Dose/fx**	**Vol.**	**Dose**	**Max. Dose**	**Protocol**	**Treated organ**	**Organ**	**Partial Organ**	**Tolerance (1.8 – 2.0 Gy/fx)**	**Critical Structure**	**Vol.**	**Dose/ Vol.**	**Max. Dose**	**Toxicity Rate**	**Toxicity Endpoint**	**Organ**	**TD 5/5**			**TD 50/5**			**Organ**	**Dose tolerance**	**End point**
Small Bowel	1.8 Gy	200 cc	30 Gy		529	Anus	Small bowel	Small volume	50 Gy	Small bowel (individual loops)	V15	<120 cc		<10%	Grade 3+ toxicity	Small intestine	4000	–	5000	5500	–	6000			
	1.8 Gy	150 cc	35 Gy		529	Anus		Whole	<40 Gy	Small bowel (peritoneal cavity)	V45	<195 cc		<10%	Grade 3+ toxicity	obstruction, perforation									
	1.8 Gy	180 cc	35 Gy		822	Rectum																			
	1.8 Gy	100 cc	40 Gy		822	Rectum																			
	1.8 Gy	20 cc	45 Gy		529	Anus																			
	1.8 Gy	65 cc	45 Gy		822	Rectum																			
	1.8 Gy			50 Gy	0822, 052 9	Rectum, anus																			
	1.8 Gy			52 Gy	PMID 18947938	RTOG Prostate Group Consensus 2009																			
	1.8 Gy	30%	40 Gy		418	Endometrial																			
Skin, longitudinal	2 Gy	50%	20 Gy		630	Sarcoma																			
Testis	2 Gy	50%	3 Gy		630	Sarcoma	Extremity	Circumferential	20-30 Gy																
Vulva	2 Gy	50%	30 Gy		630	Sarcoma	Bone marrow	Whole abdomen	<30 Gy																
Anus	2 Gy	50%	30 Gy		630	Sarcoma		Ablation	>40 Gy																
Bone, weight-bearing	2 Gy	50%	50 Gy		630	Sarcoma	Bone	Cortex	50 Gy																
Joints	2 Gy	50%	50 Gy		630	Sarcoma	Joint space	Fibrotic constriction	40-45 Gy																

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Table 5. Summary of RTOG acute toxicity criteria for head and neck region.

Tissue	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Skin	No change over baseline	Follicular, faint, or dull erythema/epilation/dry desquamation/decreased sweating	Tender or bright erythema, patchy moist desquamation/moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Mucosal membrane	No change over baseline	Injection/may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinitis discharge/may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/may include severe pain requiring narcotic	Ulceration, hemorrhage, or necrosis
Eye	No change	Mild conjunctivitis with or without scleral injection/increased tearing	Moderate conjunctivitis with or without keratitis requiring steroids and/or antibiotics/dry eye requiring artificial tears/iritis with photophobia	Severe keratitis with corneal ulceration/objective decrease in visual acuity or in visual fields/acute glaucoma/panophthalmitis	Loss of vision (unilateral or bilateral)
Ear	No change over baseline	Mild external otitis with erythema, pruritus, secondary to dry desquamation not requiring medication. Audiogram unchanged from baseline	Moderate external otitis requiring topical medication/serious otitis medius/hypoacusis on testing only	Severe external otitis with discharge or moist desquamation/symptomatic hypoacusis/tinnitus, not drug related	Deafness
Salivary gland	No change over baseline	Mild mouth dryness/slightly thickened saliva/may have slightly altered taste such as metallic taste/these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals	Moderate to complete dryness/thick, sticky saliva/markedly altered taste		Acute salivary gland necrosis
Pharynx and esophagus	No change over baseline	Mild dysphagia or odynophagia/may require topical anesthetic or non-narcotic analgesics/may require soft diet	Moderate dysphagia or odynophagia/may require narcotic analgesics/may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss (>15% from pre-treatment baseline) requiring N-G feeding tube, I.V. fluids, or hyperalimentation	Complete obstruction, ulceration, perforation, fistula
Larynx	No change over baseline	Mild or intermittent hoarseness/cough not requiring antitussive/erythema of mucosa	Persistent hoarseness but able to vocalize/referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic/cough requiring antitussive	Whispered speech, throat pain, or referred ear pain requiring narcotic/confluent fibrinous exudate, marked arytenoid edema	Marked dyspnea, stridor, or hemoptysis with tracheostomy or intubation necessary
CNS	No change	Fully functional status (i.e., able to work) with minor neurologic findings, no medication needed	Neurologic findings present sufficient to require home case/nursing assistance may be required/medications including steroids/anti-seizure agents may be required	Neurologic findings requiring hospitalization for initial management	Serious neurologic impairment which includes paralysis, coma, or seizures >3 per week despite medication/hospitalization required

Table 6. Summary of RTOG acute toxicity criteria for body region.

Organ/Tissue	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Upper G.I	No change	Anorexia with <=5% weight loss from pretreatment baseline/nausea not requiring antiemetics/abdominal discomfort not requiring parasympatholytic drugs or analgesics	Anorexia with <=15% weight loss from pretreatment baseline/nausea and/or vomiting requiring antiemetics/abdominal pain requiring analgesics	Anorexia with >15% weight loss from pretreatment baseline or requiring N-G tube or parenteral support. Nausea and/or vomiting requiring tube or parenteral support/abdominal pain, severe despite medication/hematemesis or melena/abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Ileus, subacute or acute obstruction, performation, GI bleeding requiring transfusion/abdominal pain requiring tube decompression or bowel diversion
Lower G.I	No change	Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs (e.g., Lomotil)/mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support/severe mucous or blood discharge necessitating sanitary pads/abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
Lung	No change	Mild symptoms of dry cough or dyspnea on exertion	Persistent cough requiring narcotic, antitussive agents/dyspnea with minimal effort but not at rest	Severe cough unresponsive to narcotic antitussive agent or dyspnea at rest/clinical or radiologic evidence of acute pneumonitis/intermittent oxygen or steroids may be required	Severe respiratory insufficiency/continuous oxygen or assisted ventilation
Genitourinary	No change	Frequency of urination or nocturia twice pretreatment habit/dysuria, urgency not requiring medication	Frequency of urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Pyridium)	Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvis pain, or bladder spasm requiring regular, frequent narcotic/gross hematuria with/without clot passage	Hematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration, or necrosis
Heart	No change over baseline	Asymptomatic but objective evidence of EKG changes or pericardial abnormalities without evidence of other heart disease	Symptomatic with EKG changes and radiologic findings of congestive heart failure or pericardial disease/no specific treatment required	Congestive heart failure, angina pectoris, pericardial disease responding to therapy	Congestive heart failure, angina pectoris, pericardial disease, arrhythmias not responsive to non-surgical measures

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Table 7. Summary of RTOG late toxicity criteria for head and neck regions.

Organ/Tissue	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Organ/Tissue
Subcutaneous tissue	None	Slight atrophy; pigmentation change; some hair loss	Patch atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration	Death related to radiation effects
Mucosis membrane	None	slight induration (fibrosis), and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture > 10% linear measurement	Necrosis	Death related to radiation effects
Mucosis membrane	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucous	Marked atrophy with complete dryness; severe telangiectasia	Ulceration	Death related to radiation effects
Salivary gland	None	Slight dryness of mouth; good response on stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response on stimulation	Fibrosis	Death related to radiation effects
Spinal cord	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadriplegia	Death related to radiation effects
Brain	None	Mild headache; slight lethargy	Moderate headache; great lethargy	Severe headaches; severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis; coma	Death related to radiation effects
Eye	None	Asymptomatic cataract; minor corneal ulceration or keratitis	Symptomatic cataract; moderate corneal ulceration; minor retinopathy or glaucoma	Severe keratitis; severe retinopathy or detachment severe glaucoma	Panophthalmitis/blindness	Death related to radiation effects
Larynx	None	Hoarseness; slight arytenoid edema	Moderate arytenoid edema; chondritis	Severe edema; severe chondritis	Necrosis	Death related to radiation effects

Table 8. Summary of RTOG late toxicity criteria by body region.

Organ/Tissue	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Lung	None	Asymptomatic or mild symptoms (dry cough); slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); low grade fever; patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; dense radiographic changes	Severe respiratory insufficiency/continuous O2/assisted ventilation	Death related to radiation effects
Heart	None	Asymptomatic or mild symptoms; transient T wave inversion and ST changes; sinus tachycardia >110	Moderate angina on effort; mild pericarditis; normal heart size; persistent abnormal T wave and ST changes; low ORS	Severe angina; pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement; EKG abnormalities	Tamponade/severe heart failure/severe constrictive pericarditis	Death related to radiation effects
Esophagus	None	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semi-solid food; dilation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilation required	Necrosis/perforation fistula	Death related to radiation effects
Small/large intestine	None	Mild diarrhea; mild cramping; bowel movement 5 times daily; slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement >5 times daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/perforation fistula	Death related to radiation effects
Liver	None	Mild lassitude; nausea, dyspepsia; slightly abnormal liver function	Moderate symptoms; some abnormal liver function tests; serum albumin normal	Disabling epatitis insufficiency; liver function tests grossly abnormal; low albumin; edema or ascites	Necrosis/hepatic coma or encephalopathy	Death related to radiation effects
Kidney	None	Transient albuminuria; no hypertension; mild impairment of renal function; urea 25–35 mg%; creatinine 1.5–2.0 mg%; Creatinine clearance > 75%	Persistent moderate albuminuria (2+); mild hypertension; no related anemia; moderate impairment of renal function; urea > 36–60mg%; creatinine clearance (50–74%)	Severe albuminuria; severe hypertension persistent anemia (< 10%); severe renal failure; urea > 60 mg%; creatinine > 4.0 mg%; creatinine clearance < 50%	Malignant hypotension; uremic coma/urea > 100%	Death related to radiation effects
Bladder	None	Slight epithelial atrophy; minor telangiectasia (microscopic hematuria)	Moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria	Severe frequency and dysuria; severe generalized telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (< 150 cc)	Necrosis/contracted bladder (capacity < 100 cc); severe hemorrhagic cystitis	Death related to radiation effects
Bone	None	Asymptomatic; no growth retardation; reduced bone density	Moderate pain or tenderness; growth retardation; irregular bone sclerosis moderate stiffness; intermittent or moderate joint pain; moderate limitation of movement	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis	Necrosis/spontaneous fracture	Death related to radiation effects
Joint	None	Mild joint stiffness; slight limitation of movement		Severe joint stiffness; pain with severe limitation of movement	Necrosis/complete fixation	Death related to radiation effects

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6. Radiation treatment plan analysis programs

In modern radiation therapy, physical dose indices, such as mean doses, dose-volume histograms (DVHs), and isodose distribution charts, are often used for treatment plan evaluation. DVHs provide dose volume coverage information. However, they fail to provide information regarding hot spots and dose homogeneity. When reviewing physical dose indices, the resulting biological objectives, such as tumor control rate and normal tissue complication probability, must be indirectly estimated based on clinical experience and knowledge. In some competing plans, it is possible that a similar mean dose, maximum dose, or minimum dose might have significantly different radiobiological outcomes. To facilitate the direct and accurate comparison and ranking of treatment plans, radiobiological models for treatment plan evaluation have been introduced. These radiobiological models are based on the idea that the radio-sensitivity of different organs should be taken into account. As a result, the physical dose delivered to an organ is directly associated with the dose–response probability of inducing complications in normal tissues. Many programs have been designed and developed to calculate both dosimetrical and biological indices, as shown in Table 9 [10-29].

7. Multidisciplinary strategies: Planning decision support concept

7.1. Methods could be used for planning a decision support system

In this section, we highlight dosimetrical and biological models in radiation oncology treatment planning, with focus on the methodological aspects of prediction model development. In radiation treatment planning analysis, dose volume histograms were the most widely used quantitative results. To comprehensively evaluate a certain DVH, we proposed several dosimetrical and biological models in the earlier sections. For dosimetrical models, there were PTTV, CI, and TCI for target coverage index, and MHI, HI for homogeneity index and COSI, QF, and CQI for overall index. For radiobiological models, there were TCP and NTCP for tumor or critical structures, representatively. There were still other factors like treatment time, planning time, or overall moniter unites irradiated in patients could be helpful for making more reasonable decision. Some characteristic prognostic and predictive factors like radiation-induced organ toxicities were discussed in earlier sections. We also enumerate the normal tissue tolerance criteria including QUENTEC and EMAMI database.

7.2. The need of plan decision support concept in RT

With the emergence of individualized medicine and the increasing amount and complexity of available medical data, a growing need exists for the development of planning decision-support systems based on prediction models of treatment outcome [55-57]. In radiation oncology, these models combine both predictive and prognostic data factors from dosimetrical, biological, imaging, and other sources to achieve the highest accuracy to predict tumor response and follow-up event rates. The central challenge, however, is how to integrate diverse, multimodal information (imaging, dosimetrical, biological, and other data) in a quantitative manner to provide specific clinical predictions that accurately and robustly

estimate patient outcomes as a function of the possible decisions. Currently, many prediction models are being published that consider factors related to disease and treatment, but without standardized assessments of their robustness, reproducibility, or clinical utility [58]. Consequently, these prediction models might not be suitable for clinical decision-support systems for routine care.

Review of previous programs

	Input system			Dicom RT platform		Plan comparison						Plan analysis			Program features		Paper publication			
						Physical		Biological				Statistical analysis								
Program	Patient information	Data format	Data compatibility	Compatible with PACS	3D image module	DVH calculator	Physical index	TCP/NTCP	Overall	Multi-RTP	Analysis database	Normal statistic	Survival statistic	Independence from GUI	Platform	Author	Paper	Year	Others
HART	×	AAPM/ RTOG, DicomRT	Pinnacle	×	√	√	√	√	×	×	×	×	×	×	MatLab	Anil Pyakuryal	(23)	2010	http://www2.uic.edu/~apyaku1/
CERR	×	AAPM/ RTOG, DicomRT (toolbox)	Pinnacle, expand function with DicomRT toolbox	×	√	√	×	×	×	×	√	×	×	√	MatLab, Fortran, C/C++, Java	Joseph O. Deasy	(10)	2003	http://www.cerr.info/about.php
DREES	√	Matlab's human-readable data structures	No	×	×	×	×	√	×	×	×	×	√	×	MatLab	Joseph O. Deasy	(11)	2006	http://cerr.info/drees/about.php
EUD-based mathematical model	×	DVH file	specialized format	×	×	×	×	√	×	×	×	×	×	×	MatLab	Andrzej Niemierko	(12)	2007	-
EUCLID	√	AAPM/ RTOG, DicomRT	LANTIS and IMPAC based on DRESS	×	×	×	×	√	×	×	×	×	√	×	MatLab	Olivier Gayou	(13)	2007	-
Dose Volume Histogram Analyzer	×	Eclipse, Pinnacle, Tomo, DVH files	Eclipse, Pinnacle, Tomo	×	×	×	×	√	×	×	×	×	×	×	MatLab	Jin Sung Kim	(17)	2008	http://mpjinsung.tistory.com/entry/DVH-Analyzer-v10

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Review of previous programs																		
	Input system			Dicom RT platform		Plan comparison					Plan analysis			Program features	Paper publication			
Program	Patient information	Data format	Data compatibility	Compatible with PACS	3D image module	Physical		Biological	Overall	Multi-RTP	Analysis database	Statistical analysis		Independence from GUI	Platform	Author	Paper	Year	Others
						DVH calculator	Physical index	TCP/NTCP				Normal statistic	Survival statistic						
computational platform	√	AAPM/ RTOG, DicomRT	compatible with ARIA, different RTP	√	√	×	×	√	×	×	√	×	√	√	MatLab, Web, ARIA	Dezhi Liu	(18)	2009	-
BIOPLAN	×	DVH file	DVH file	×	×	×	×	√	×	×	×	×	×	×	Microsoft Visual Basic	B. SANCHEZ -NIETO	(52)	2000	-
Anonymous	×	DVH file	DVH file	×	×	×	×	√	×	×	×	×	×	×	MatLab	Arun S. Oinam	(21)	2011	-
SlicerRT	√	Dicom RT	compatible with cormercial RTP	×	√	×	×	√	×	×	×	×	×	√	C++	Csaba Pinter	(22)	2012	https://www.assembla.com/spaces/slicerrt/wiki
MERT	√	Dicom RT	This was RTP	×	√	√	×	√	×	×	×	×	×	√	Multi format(MC)	Murat Surucu	(26)	2010	-
DIRART	×	Dicom RT	use CERR import engine	×	√	×	×	√	×	×	×	×	×	√	MatLab	Deshan Yang	(27)	2010	http://code.google.com/p/dirart/
SABER	×	Dicom RT	Eclipse	×	×	×	×	√	×	×	×	×	×	×	MatLab	Jay Burmeister	(29)	2010	-
DICOM RT toolbox	√	Dicom RT	Helax TMS	×	√	√	×	×	×	×	×	×	×	×	MatLab	Spezi E	(24)	2002	-

Table 9. Review of previous programs

Review of previous programs																		
	Input system			Dicom RT platform		Plan comparison						Plan analysis			Program features	Paper publication			
Program	Patient information	Data format	Data compatibility	Compatible with PACS	3D image module	Physical		Biological	Overall	Multi-RTP	Analysis database	Statistical analysis		Independence from GUI	Platform	Author	Paper	Year	Others
						DVH calculator	Physical index	TCP/NTCP				Normal statistic	Survival statistic						
BEUDcal	×	DVH file	DVH file	×	×	√	×	√	×	×	×	×	×	×	MatLab	Su FC	(25)	2010	_
Comp Plan	×	DVH file	DVH file in Excel	×	×	×	×	√	×	×	×	×	×	×	MatLab	Holloway LC	(15)	2012	_
CalcNTCP	×	Manual input	Manual input	×	×	×	×	√	×	×	×	×	×	×	Visual Basic	Khan HA	(16)	2007	_
RADBIOMOD	×	DVH file	Manual input	×	×	×	√	√	×	×	×	×	×	×	Microsoft Ecel	Chang JH	(53)	2011	https://sites.google.com/site/radbiomod/home
BioSuite	×	DVH file	Pinnacle, Eclups	×	×	√	×	√	×	×	×	×	×	√	C++	J Uzan	(54)	2012	_
RTToolbox	√	Dicom RT	Virtuos, our in-house developed planning system	×	√	√	×	√	×	×	√	×	×	√	C++	Lanlan, Zhang	(28)	2013	_

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Decision making in radiotherapy is mainly based on clinical features, such as the patient performance status, organ function, and grade and extent of the tumor (e.g., as defined by the TNM system). In almost all studies, such features have been found to be prognostic for survival and development of toxicity [59, 60]. Consequently, these features should be evaluated in building robust and clinically acceptable radiotherapy prognostic and predictive models. Moreover, measurement of some clinical variables, such as performance status, can be captured with minimal effort.

Toxicity measurements and scoring should also build on validated scoring systems, such as the Common Terminology Criteria for Adverse Events (CTCAE), which can be scored by the physician or patient [50, 61]. Indeed, a meta-analysis showed that high-quality toxicity assessments from observational trials are similar to those of randomized trials. [45, 46] However, a prospective protocol must clarify which scoring system was used and how changes in toxicity score were dealt with over time with respect to treatment. Finally, to ensure a standardized interpretation, the reporting of clinical and toxicity data and their analyses should be performed in line with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for observational studies and genetic-association studies, which is represented as checklists of items that should be addressed in reports to facilitate the critical appraisal and interpretation of these types of studies (Figure 7).

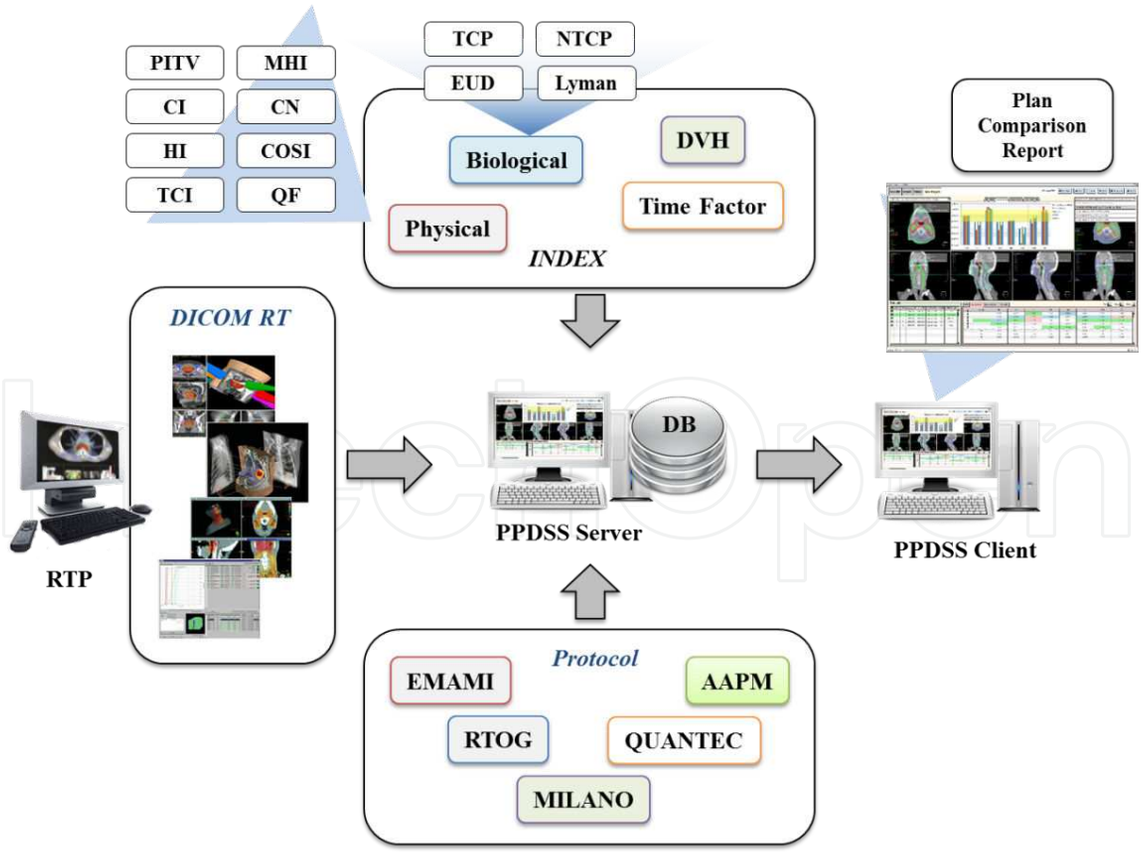

Figure 7. Design of planning decision support concept in radiotherapy treatment planning.

Despite the challenges that remain, the vision of predictive models leading to plan decision support concept that are continuously updated via rapid learning on large datasets is clear, and numerous steps have already been taken. These include universal data-quality assurance programs and semantic interoperability issues. However, we believe that this truly innovative journey will lead to necessary improvement of healthcare effectiveness and efficiency. Indeed, investments are being made in research and innovation for health-informatics systems, with an emphasis on interoperability and standards for secured data transfer, which shows that "eHealth" will be among the largest health-care innovations of the coming decade. Accurate, externally validated prediction models are being rapidly developed, whereby multiple features related to the patient's disease are combined into an integrated prediction. The key, however, is standardization—mainly in data acquisition across all areas, including dosimetrical-based and biological-based models, patient preferences, and possible treatments. These crucial features are the basis of validating a plan decision support system, which, in turn, will stimulate developments in rapid-learning health care and will enable the next major advances in shared decision making.

8. Conclusion

Plan comparison studies still remain controversial. The main reason for this is because plan parameters, optimization methods, and OAR constraints are difficult to clearly define. Many researchers have focused on the influence of planning parameters on the results of treatment plans [62-64]. For instance, Gutiérrez et al. [65] reported that the use of a field width of 1 cm resulted in dosimetrically superior plans for brain irradiation compared to plans that use a field width of 2.5 cm. More recently, Skorska and Piotrowski studied the influence of treatment-planning parameters on plan qualities for prostate cancer patients using helical tomotherapy [66]. This study revealed that using a field width of 1 cm, instead of 5 cm, leads to decreases in the D20%, D40%, D60%, and D80% of the small intestine by 2.45%, 8.48%, 6.36%, and 5%. This results in 1.22Gy, 4.24Gy, 3.18Gy, and 2.50Gy, respectively, for the prescribed dose of 50 Gy. Another bias of plan comparison studies is that the quality of a planner's abilities and planning techniques may vary. Performing repeat planning processes and using multiple planners to cross check would minimize such bias. The use of OAR dose tolerance guidelines, such as RTOG or QUENTEC protocols, would minimize human error.

Other major issues among plan comparison studies are the method of plan analysis and evaluation. Many studies have focused on developing a simple index that represents the overall quality of plans [14, 19, 41, 42, 67]. However, none of these plans are easily used in a clinic. There is a need for programs that can easily calculate dosimetrical and biological indices [10, 12, 13, 15, 16, 22-25, 28, 68, 78-82].

There is a growing trend of studying the relationships between treatment plan results and clinical outcomes, such as toxicities, survival, and patterns of failure [69-77]. Such studies may help physicians and physicists learn more about the influence of plan results and plan quality on patient treatment.

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