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Chapter 5

Physical and Radiobiological Evaluation of Radiotherapy Treatment Plan

Suk Lee, Yuan Jie Cao and Chul Yong Kim

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 dosimetric 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 dosimetric 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 dosimetric 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].
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 dosimetrist 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.

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
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 dosimetric and biological indices since the 2000s [10-29]. This is shown in Figure 3.

<table>
<thead>
<tr>
<th>Treatment planning system</th>
<th>Company</th>
<th>Website</th>
</tr>
</thead>
<tbody>
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</tr>
</tbody>
</table>

Table 1. Commercial RTP lists
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...
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.
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 ($V_{\text{L}}$ to $V_{\text{H}}$), IMPT was more favorable than HT. However, this relationship reversed for high dose volume ($V_{\text{H}}$ to $V_{\text{L}}$). As a result, there are several indexes that may represent target conformity and dose homogeneity [31, 35-38].

4.1. Dosimetric 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:

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

(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:

$$CI = \frac{PTV_{\text{PD}}}{PIV}$$

(2)
In the above equation, PIV represents prescription isodose surface volume and PTV\textsubscript{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:

\[
HI = \frac{D_{\text{max}}}{PD}
\]  

(3)

In the above equation, \(D_{\text{max}}\) 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:

\[
TCI = \frac{PTV_{PD}}{PTV}
\]  

(4)

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

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

\[
MHI = \frac{D_{95}}{D_5}
\]  

(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:

\[
CN = TCI \times CI = \frac{PTV_{PD}}{PTV} \times \frac{PTV_{PD}}{PIV}
\]  

(6)

In the above equation, PTV\textsubscript{PD} refers to PTV coverage at the prescription dose and PIV represents prescription isodose surface volume [42].
<table>
<thead>
<tr>
<th>Index</th>
<th>Formula</th>
<th>Concept</th>
<th>Value = 1</th>
<th>Value &lt;1 or value &gt;1</th>
</tr>
</thead>
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<td>$PTV_{PD}$</td>
<td>$PTV_{PD}$</td>
<td>$PTV_{PD}$</td>
</tr>
<tr>
<td>CI (conformity index)</td>
<td>$CI = \frac{PTV_{PD}}{PTV}$</td>
<td>$PTV_{PD}$</td>
<td>$PTV_{PD}$</td>
<td>$PTV_{PD}$</td>
</tr>
<tr>
<td>TCI (target coverage index)</td>
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<td>$PTV_{PD}$</td>
<td>$PTV_{PD}$</td>
<td>$PTV_{PD}$</td>
</tr>
<tr>
<td>CN (conformity number)</td>
<td>$CN = (CI + CI) = \frac{PTV_{PD}}{PTV}$</td>
<td>$PTV_{PD}$</td>
<td>$PTV_{PD}$</td>
<td>$PTV_{PD}$</td>
</tr>
<tr>
<td>HI (homogeneity index)</td>
<td>$HI = \frac{D_{min}}{PD}$</td>
<td></td>
<td>Maximum dose</td>
<td>Maximum dose</td>
</tr>
<tr>
<td>MHI (modified homogeneity index)</td>
<td>$MHI = \frac{D_{max}}{D_{min}}$</td>
<td></td>
<td>Maximum dose</td>
<td>Maximum dose</td>
</tr>
<tr>
<td>COSI (critical organ scoring index)</td>
<td>$COSI = 1 - \sum \frac{PTV_{PD}}{PTV_{PD}}$</td>
<td>$PTV_{PD}$</td>
<td>$PTV_{PD}$</td>
<td>$PTV_{PD}$</td>
</tr>
</tbody>
</table>

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

\[ EUD = \left( \sum_{i=1}^{n} \left( V_i \cdot EQD_i \right)^{a} \right)^{1/a} \]  

(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 \( \alpha \), 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:

\[ EQD = D \times \left( \frac{\alpha + D}{\beta + V_i} \right) \]  

(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, \( \alpha/\beta \) is the tissue-specific linear quadratic (LQ) parameter of the organ being exposed. Niemierko’s TCP [12] is defined as:

\[ TCP = \frac{1}{1 + \left( \frac{TCD_{50}}{EUD} \right)^{\gamma_{50}}} \]  

(9)

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

\[ TCP = \frac{1}{1 + \left( \frac{TCD_{50}}{EUD} \right)^{\gamma_{50}}} \]  

(10)
where $TD_{ro}$ 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]:

$$CQI = \frac{1}{N} \sum_{i=1}^{N} QI_i = \frac{1}{N} \sum_{i=1}^{N} \left( \frac{D_{\text{max}}^{\text{plan}}}{D_{\text{max}}^{\text{max}}} \right)$$

(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:

$$COSI = 1 - \sum \frac{V_i(OAR)^{\text{ref}}}{TCV}$$

(12)

where $V_i(OAR)^{\text{ref}}$ 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:

$$mCOSI = \sum W_i \left( \frac{COSI_{10} + COSI_{20} + \cdots + COSI_{80}}{8} \right)$$

(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.
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:

$$ QF = \left[ 2.718 \exp\left( -\sum_{i=1}^{N} W_i X_i \right) \right] $$ (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.
<table>
<thead>
<tr>
<th>Critical Structure</th>
<th>RTG data</th>
<th>QUANTEC data</th>
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<td>50 Gy</td>
<td>615</td>
<td>Nasopharynx</td>
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<td>50 Gy</td>
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<tr>
<td>Optic chiasm</td>
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</tr>
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<td>Optic chiasm</td>
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<tr>
<td>54 Gy (0.03 cc)</td>
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<tr>
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<tr>
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<td>0390, 0615</td>
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<td>Oral cavity (non-involved)</td>
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<td>2 Gy</td>
<td>Mean &lt;30 Gy</td>
<td>60 Gy</td>
<td>1016</td>
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### Table 2. Radiation tolerance dose in head and neck

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<th>Critical Structure</th>
<th>Dose/ fx</th>
<th>Vol.</th>
<th>Dose</th>
<th>Max. Dose</th>
<th>Protocol</th>
<th>Radiation dose</th>
<th>Toxicity Rate</th>
<th>Toxicity Endpoint</th>
<th>Organ</th>
<th>TD 5/5</th>
<th>TD 50/5</th>
<th>Organ</th>
<th>Dose Tolerance</th>
<th>Endpoint</th>
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<td>2 Gy</td>
<td>Mean</td>
<td>&lt;2 Gy</td>
<td>0619, 0522, 1016</td>
<td>Postop H&amp;N, definitive H&amp;N, oropharynx</td>
<td>Mean &lt;25 Gy</td>
<td>&lt;20%</td>
<td>Long-term salivary function &lt;25%</td>
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<td>V50</td>
<td>one</td>
<td>&lt;50 Gy gland</td>
<td>0619, 0522</td>
<td>Postop H&amp;N, definitive H&amp;N</td>
<td>Mean &lt;39 Gy</td>
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<td>Long-term salivary function &lt;25%</td>
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<td>Mean</td>
<td>Unilateral</td>
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<td>Postop H&amp;N, definitive H&amp;N</td>
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<td>Long-term salivary function &lt;25%</td>
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<td>50 Gy</td>
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<td>Pharyngeal constrictors</td>
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<td>15%</td>
<td>60 Gy</td>
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<td>Mean</td>
<td>40 Gy</td>
<td>1016</td>
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<td>50 Gy</td>
<td>Mean</td>
<td>0.03 cc</td>
<td>0539, 0825, 0615</td>
<td>High-risk meningioma, glioblastoma, nasopharynx</td>
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<td>Mean</td>
<td>4 Gy</td>
<td>0523, 0615</td>
<td>4500</td>
<td>–</td>
<td>–</td>
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<td><strong>Spinal Cord</strong></td>
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<td>4 Gy</td>
<td>Mean</td>
<td>0523, 0615</td>
<td>Lung, Nasopharynx</td>
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<td>48 Gy</td>
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<td>Postop H&amp;N, definitive H&amp;N, Spinal cord</td>
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<tr>
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<td>Mean</td>
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<td>Myelopathy</td>
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<td>4 Gy</td>
<td>Mean</td>
<td>&lt;30 Gy</td>
<td>0615</td>
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### Analysis

- **Parotid Glands**: Mean dose tolerance for a single gland is <25 Gy with a toxicity rate of <20% for long-term salivary function. For bilateral parotid glands, the mean dose is <39 Gy with a toxicity rate of <50% for long-term salivary function.
- **Pharynx, postcricoid**: The mean dose for 45 Gy is 665 with a toxicity rate of <20% for symptomatic dysphagia and aspiration.
- **Retina**: The mean dose for 4 Gy is 0.03 cc with intermediate risk meningioma. For high-risk meningioma, glioblastoma, and nasopharynx, the mean dose is 4 Gy with a toxicity rate of <50 Gy for myelopathy.
- **Spinal Cord**: The mean dose for 4 Gy is 0.03 cc with lung and nasopharynx. For spinal cord, the mean dose is <50 Gy with a toxicity rate of <20% for myelopathy (20cm) (10cm) (5 cm).
<table>
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<tr>
<th>Treated organ</th>
<th>TD 5/5</th>
<th>Vol.</th>
<th>Dose/Vol.</th>
<th>Max. Dose</th>
<th>Toxicity Rate</th>
<th>Toxicity Endpoint</th>
<th>TD 0/5</th>
<th>TD 50/5</th>
<th>TD 95/5</th>
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<td>Mean</td>
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<tr>
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<td>Small bowel (peritoneal cavity)</td>
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<td>40 Gy</td>
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<td>TD 5/5</td>
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<td>45 Gy</td>
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<td>&lt;7%</td>
<td>Ulceration</td>
<td>TD 5/5</td>
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<td>Vol.</td>
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<td>Max. Dose</td>
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Evolution of Ionizing Radiation Research
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**External genitalia**
- **Critical Structure**: 1.8 Gy
- **Dose/fx**: 30 Gy
- **Vol.**: 529 Anus
- **Dose**: 529 Anus
- **Max. Dose**: 529 Anus
- **Protocol**: Adult
- **Treated organ**: Femoral head

**Femoral Head**
- **Critical Structure**: 1.8 Gy
- **Dose/fx**: 30 Gy
- **Vol.**: 529 Anus
- **Dose**: 529 Anus
- **Max. Dose**: 529 Anus
- **Protocol**: Reochia

**Bladder**
- **Critical Structure**: 1.8 Gy
- **Dose/fx**: 30 Gy
- **Vol.**: 529 Anus
- **Dose**: 529 Anus
- **Max. Dose**: 529 Anus
- **Protocol**: Reochia

**Large Bowel**
- **Critical Structure**: 1.8 Gy
- **Dose/fx**: Mean
- **Vol.**: 52.5 Gy
- **Dose**: 415 Prostate
- **Max. Dose**: 415 Prostate
- **Protocol**: Reochia

**Penile Bulb**
- **Critical Structure**: 1.8 Gy
- **Dose/fx**: Mean
- **Vol.**: 52.5 Gy
- **Dose**: 415 Prostate
- **Max. Dose**: 415 Prostate
- **Protocol**: Reochia
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<td>Skin</td>
<td>No change over baseline</td>
<td>Follicular, faint, or dull erythema/epilation/dry desquamation/decreased sweating</td>
<td>Tender or bright erythema, patchy moist desquamation/mild edema</td>
<td>Confluent, moist desquamation other than skin folds, pitting edema</td>
<td>Ulceration, hemorrhage, necrosis</td>
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<tr>
<td>Mucosal membrane</td>
<td>No change over baseline</td>
<td>Injection/may experience mild pain not requiring analgesic</td>
<td>Patchy maculopapular erythema which may produce an inflammatory response</td>
<td>Patchy maculopapular erythema may include severe pain requiring analgesic</td>
<td>Ulceration, hemorrhage, necrosis</td>
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<td>Eye</td>
<td>No change over baseline</td>
<td>Mild conjunctivitis with or without chemosis/increased tearing</td>
<td>Moderate conjunctivitis with or without keratitis requiring steroids</td>
<td>Severe keratitis with corneal ulcération/objective decrease in visual acuity or in visual fields/acute glaucoma/papilledema</td>
<td>Ulceration, hemorrhage, necrosis</td>
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<td>Ear</td>
<td>No change over baseline</td>
<td>Mild external otitis with or without chemosis/increased tearing</td>
<td>Moderate external otitis requiring topical medication/severe otitis</td>
<td>Severe external otitis with discharge or moist desquamation/symptomatic hypoacusis</td>
<td>Deafness</td>
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<td>Salivary gland</td>
<td>No change over baseline</td>
<td>Mild mouth dryness/slightly thickened saliva/taste such as metallic taste</td>
<td>Moderate to complete dryness/thick, sticky saliva/markedly altered taste</td>
<td>Acute salivary gland necrosis</td>
<td>Acute salivary gland necrosis</td>
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<td>Pharynx and esophagus</td>
<td>No change over baseline</td>
<td>Mild dysphagia or odynophagia/may require topical analgesic</td>
<td>Moderate dysphagia or odynophagia/may require narcotic/non-narcotic analgesics/may require soft diet</td>
<td>Severe dysphagia or odynophagia with dehydration or weight loss (&gt;15% from pre-treatment baseline) requiring N-G feeding tube, I.V. fluids, or hyperalimentation</td>
<td>Complete obstruction, ulceration, perforation, fistula</td>
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<td>Larynx</td>
<td>No change over baseline</td>
<td>Mild or intermittent hoarseness/cough not requiring analgesic/bright erythema of mucosa</td>
<td>Persistent hoarseness but able to vocalize/referred ear pain, sore throat, patchy/irritative exudate or mild arytenoid edema not requiring narcotic/cough requiring antitussive</td>
<td>Whispered speech, throat pain, or referred ear pain requiring narcotic/confluent irritative exudate, marked arytenoid edema</td>
<td>Marked dyspnea, stridor, or hemoptysis with tracheostomy or intubation necessary</td>
</tr>
</tbody>
</table>
| CNS                       | No change over baseline                                                 | Fully functional status (i.e., able to work) with minor neurologic findings, no medication needed | Neurologic findings present sufficient to require home care/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
<table>
<thead>
<tr>
<th>Organ/Tissue</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper G.I</td>
<td>No change</td>
<td>Anorexia with &lt;=5% weight loss from pretreatment baseline/nausea not requiring antiemetics/abdominal discomfort not requiring parasympatholytic drugs or analgesics</td>
<td>Anorexia with &lt;=15% weight loss from pretreatment baseline/nausea and/or vomiting requiring antiemetics/abdominal pain requiring analgesics</td>
<td>Anorexia with &gt;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)</td>
<td>Ileus, subacute or acute obstruction, perforation, GI bleeding requiring transfusion/abdominal pain requiring tube decompression or bowel diversion</td>
</tr>
<tr>
<td>Lower G.I</td>
<td>No change</td>
<td>Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics</td>
<td>Diarrhea requiring parasympatholytic drugs (e.g., Lomotil)/mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics</td>
<td>Severe cough unresponsive to narcotic antitussive agent or dyspnea at rest</td>
<td>Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion</td>
</tr>
<tr>
<td>Lung</td>
<td>No change</td>
<td>Mild symptoms of dry cough or dyspnea on exertion</td>
<td>Persistent cough requiring narcotic, antitussive agents/dyspnea with minimal effort but not at rest</td>
<td>Severe cough unresponsive to narcotic antitussive agent or dyspnea at rest</td>
<td>Severe respiratory insufficiency/continuous oxygen or assisted ventilation</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>No change</td>
<td>Frequency of urination or nocturia twice pretreatment habit/dysuria, urgency not requiring medication</td>
<td>Frequency of urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Pyridium)</td>
<td>Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvis pain, or bladder spasm requiring regular, frequent narcotic/gnss hematuria with/without clot passage</td>
<td>Hematuria requiring emergency transfusion/acute bladder obstruction not secondary to clot passage, ulceration, or necrosis</td>
</tr>
<tr>
<td>Heart</td>
<td>No change over baseline</td>
<td>Asymptomatic but objective evidence of EKG changes or pericardial abnormalities without evidence of other heart disease</td>
<td>Symptomatic with EKG changes and radiologic findings of congestive heart failure or pericardial disease/no specific treatment required</td>
<td>Congestive heart failure, angina pectoris, pericardial disease responding to therapy</td>
<td>Congestive heart failure, angina pectoris, pericardial disease, arrhythmias not responsive to nonsurgical measures</td>
</tr>
<tr>
<td>Organ/Tissue</td>
<td>Grade 0</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>Subcutaneous tissue</td>
<td>None</td>
<td>Slight atrophy; pigmentation change; some hair loss</td>
<td>Patch atrophy; moderate telangiectasia; total hair loss</td>
<td>Marked atrophy; gross telangiectasia</td>
<td>Ulceration</td>
</tr>
<tr>
<td>Mucosis membrane</td>
<td>None</td>
<td>Slight induration (fibrosis), and loss of subcutaneous fat</td>
<td>Moderate fibrosis but asymptomatic; slight field contraction; &lt;10% linear reduction</td>
<td>Severe induration and loss of subcutaneous tissue; field contraction &gt; 10% linear measurement</td>
<td>Necrosis</td>
</tr>
<tr>
<td>Mucosis membrane</td>
<td>None</td>
<td>Slight atrophy and dryness</td>
<td>Moderate atrophy and telangiectasia; little mucous</td>
<td>Marked atrophy with complete dryness; severe telangiectasia</td>
<td>Ulceration</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>None</td>
<td>Slight dryness of mouth; good response on stimulation</td>
<td>Moderate dryness of mouth; poor response on stimulation</td>
<td>Complete dryness of mouth; no response on stimulation</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>None</td>
<td>Mild L’Hermitte’s syndrome</td>
<td>Severe L’Hermitte’s syndrome</td>
<td>Objective neurological findings at or below cord level treated</td>
<td>Mono, para quadriplegia</td>
</tr>
<tr>
<td>Brain</td>
<td>None</td>
<td>Mild headache; slight lethargy</td>
<td>Moderate headache; great lethargy</td>
<td>Severe headaches; severe CNS dysfunction (partial loss of power or dykinesia)</td>
<td>Seizures or paralysis; coma</td>
</tr>
<tr>
<td>Eye</td>
<td>None</td>
<td>Asymptomatic cataract; minor corneal ulceration or keratitis</td>
<td>Symptomatic cataract; moderate corneal ulceration; minor retinopathy or glaucoma</td>
<td>Severe keratitis; severe retinopathy or detachment severe glaucoma</td>
<td>Panophthalmitis/blindness</td>
</tr>
<tr>
<td>Larynx</td>
<td>None</td>
<td>Hoarseness; slight arytenoid edema</td>
<td>Moderate arytenoid edema; chondritis</td>
<td>Severe edema; severe chondritis</td>
<td>Necrosis</td>
</tr>
</tbody>
</table>

Table 7. Summary of RTOG late toxicity criteria for head and neck regions.
### Grade 0
- **Lung**: None
- **Heart**: None
- **Esophagus**: None
- **Small/large intestine**: None
- **Liver**: None
- **Kidney**: None
- **Bladder**: None
- **Bone**: None
- **Joint**: None

### Grade 1
- **Lung**: Asymptomatic or mild symptoms (dry cough); slight radiographic appearances
- **Heart**: Asymptomatic or mild symptoms; transient T wave inversion and ST changes; sinus tachycardia >110
- **Esophagus**: Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing
- **Small/large intestine**: Mild diarrhea; mild cramping; bowel movement 5 times daily; slight rectal discharge or bleeding
- **Liver**: Mild lassitude; nausea, dyspepsia; slightly abnormal liver function
- **Kidney**: Transient albuminuria; no hypertension; mild impairment of renal function; urea 25–35 mg%; creatinine 1.5–2.0 mg%; creatinine clearance > 75%
- **Bladder**: Slight epithelial atrophy; minor telangiectasia (microscopic hematuria)
- **Bone**: Asymptomatic; no growth retardation; reduced bone density
- **Joint**: Mild joint stiffness; slight limitation of movement

### Grade 2
- **Lung**: Moderate symptomatic fibrosis or pneumonitis (severe cough); low grade fever; patchy radiographic appearances
- **Heart**: Moderate angina on effort; mild pericarditis; normal heart size; persistent abnormal T wave and ST changes; low ORS
- **Esophagus**: Unable to take solid food normally; swallowing semi-solid food; dilation may be indicated
- **Small/large intestine**: Moderate diarrhea and colic; bowel movement >5 times daily; excessive rectal mucus or intermittent bleeding
- **Liver**: Moderate symptoms; some abnormal liver function tests; serum albumin normal
- **Kidney**: Persistent moderate albuminuria (2+); mild hypertension; no related anemia; moderate impairment of renal function; urea > 36–60 mg%; creatinine clearance (50–74%)
- **Bladder**: Moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria
- **Bone**: Moderate pain or tenderness; growth retardation; irregular bone sclerosis
- **Joint**: Moderate stiffness; intermittent or moderate joint pain; moderate limitation of movement

### Grade 3
- **Lung**: Severe symptomatic fibrosis or pneumonitis; dense radiographic changes
- **Heart**: Severe angina; pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement; EKG abnormalities
- **Esophagus**: Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilation required
- **Small/large intestine**: Obstruction or bleeding, requiring surgery
- **Liver**: Severe hepatitis insufficiency; liver function tests grossly abnormal; low albumin; edema or ascites
- **Kidney**: Severe albuminuria; severe hypertension; persistent anemia (< 10%); severe renal failure; urea > 60 mg%; creatinine > 4.0 mg%; creatinine clearance < 50%
- **Bladder**: Severe frequency and dysuria; severe generalized telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (< 150 cc)
- **Bone**: Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis
- **Joint**: Severe joint stiffness; pain with severe limitation of movement

### Grade 4
- **Lung**: Severe respiratory insufficiency/continuous O2/assisted ventilation
- **Heart**: Tamponade/severe heart failure/severe constrictive pericarditis
- **Esophagus**: Necrosis/perforation fistula
- **Small/large intestine**: Necrosis/perforation fistula
- **Liver**: Necrosis/hepatic coma or encephalopathy
- **Kidney**: Malignant hypotension; uremic coma/urea > 100%
- **Bladder**: Necrosis/contracted bladder (capacity < 100 cc); severe hemorrhagic cystitis
- **Bone**: Necrosis/spontaneous fracture
- **Joint**: Necrosis/complete fixation

### Grade 5
- **Lung**: Death related to radiation effects
- **Heart**: Death related to radiation effects
- **Esophagus**: Death related to radiation effects
- **Small/large intestine**: Death related to radiation effects
- **Liver**: Death related to radiation effects
- **Kidney**: Death related to radiation effects
- **Bladder**: Death related to radiation effects
- **Bone**: Death related to radiation effects
- **Joint**: Death related to radiation effects
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 monitor units 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. Consequently, these prediction models might not be suitable for clinical decision-support systems for routine care.

<table>
<thead>
<tr>
<th>Program</th>
<th>Input system</th>
<th>Dicom RT platform</th>
<th>Plan comparison</th>
<th>Plan analysis</th>
<th>Disease features</th>
<th>Paper publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>HART</td>
<td>AAPM/RTDOG, DicomRT</td>
<td>Pinnacle</td>
<td>×</td>
<td>×</td>
<td>×</td>
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</tr>
<tr>
<td>CERR</td>
<td>AAPM/RTDOG, DicomRT</td>
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<td>×</td>
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<td>DVH-3d</td>
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<td>ECCLID</td>
<td>AAPM/RTDOG, LASSIE, and IMPAC</td>
<td>DicomRT, DICOM</td>
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<td>Dose Volume Histogram Analyzer</td>
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<td>Jin Sung Kim (15)</td>
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</tbody>
</table>

Evolution of Ionizing Radiation Research
<table>
<thead>
<tr>
<th>Program</th>
<th>Input system</th>
<th>DICOM RT platform</th>
<th>Plan comparison</th>
<th>Plan analysis</th>
<th>Program features</th>
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<td>Use CERR import engine</td>
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<td>Eclipse</td>
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<td>DICOM RT tools</td>
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<td>Helas TMS</td>
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</table>

Review of previous programs

- **Physical and Radiobiological Evaluation of Radiotherapy Treatment Plan**
  - DOI: 10.5772/60846

**Physical platform**
- AAPM
- DicomRT
- ARIA

**Biological platform**
- TCP/NTCP
- Normal statistic
- Survival statistic

**Dependency from GUI**
- Independence from GUI

**Platforms**
- Matlab
- Web
- ARIA

**Others**
- C++
- Visual Basic

**Authors**
- Dezhi Liu (2009)
- B. Sanchez-Nieto (2000)
- Aran S. Oinam (2011)
- Csaba Pinter (2012)
- Murat Surucu (2010)
- Deshan Yang (2010)
- Jay Burmeister (2010)
- Speal E (2002)
<table>
<thead>
<tr>
<th>Program</th>
<th>Patient information</th>
<th>Data format</th>
<th>Data compatibility</th>
<th>3D image module</th>
<th>Compatible with PACS</th>
<th>DVH calculator</th>
<th>Physical index</th>
<th>Physical - TCP/NTCP</th>
<th>Biological - Overall</th>
<th>Multi-RTP</th>
<th>Analysis database</th>
<th>Statistical analysis</th>
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<th>Independence from GUI</th>
<th>Platform</th>
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<td>DVH file</td>
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<td>×</td>
<td>×</td>
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</table>
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).

![Diagram of planning decision support concept in radiotherapy treatment planning.](http://dx.doi.org/10.5772/60846)

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 dosimetric-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 dosimetical 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.
Acknowledgements

This chapter was developed by a special working group of the Korea University Medical Physics Lab from the department of radiation oncology, college of medicine, Korea University, Seoul, 136-705, Korea. Members of the planning index study working group include Kwang Hyeon Kim, M.S., Kyung Hwan Chang, Ph.D., and Jang Bo Shim, M.S.

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Department of Radiation Oncology, College of Medicine, Korea University, Seoul, Korea

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