

## Background

A balance between patient accrual and uniformity of dose distributions must be achieved when writing the dose prescription for cooperative group clinical trials. Writing the prescription to accommodate a large variation in the quality of acceptable treatment plans (determined by metrics like, for example, the mean dose for the PTV, the percentage of the PTV covered by a stated dose, and the dose heterogeneity within the PTV) can improve accrual, but will increase uncertainty in the exact dose delivered so that accrual numbers must be increased. Thus, writing the prescription for any clinical trial is a critical part of protocol design.

Variation in radiation therapy treatment plans can occur for a number of reasons. Some of the variation can be controlled, while other factors are more difficult to eliminate. For example, plan quality can vary simply due to the way the treatment plan is calculated. If large grid spacing is used for the dose calculation, the quality of the resulting dose distribution will degrade compared to a calculation with a smaller grid size. At the expense of calculation time, this problem is easily controlled. Additionally, treatment plan quality in terms of adherence to a stated prescription can vary because the desired prescription is not clearly and/or completely presented in the protocol. This source of error is also easily handled by restating the prescription more clearly. Another source of variation in treatment plans for a particular treatment situation is the geometric differences that can occur. An example here is the situation where the tumor extension results in a more difficult geometrical relationship relative to nearby critical structures. This problem illustrates the major difficulty of writing the dose prescription for clinical trials. It is important to state the prescription so that this subgroup of patients can be accrued to the protocol, while not allowing inferior treatment plans to be accepted for patients that do not present a particularly difficult geometrical relationship between the target volume(s) and surrounding critical structures.

In order to deal with this problem, The RTOG uses a two part statement of the dose prescription:

1. The *per protocol* prescription is used to encourage institutions to devise treatment plans that are as tight as possible in terms of dose conformality for PTV coverage.
2. The *variation acceptable* compliance criterion is given to allow leeway for more difficult treatment planning situations.

In each protocol the *variation acceptable* dose limits should be identified as being less desirable, but allowed in situations where per protocol limits could not be met. It is important to point out here that the *variation acceptable* criterion should not be used for misinterpreting the statement of the prescription. If an institution applies the prescription incorrectly, a third category called *deviation unacceptable* is used. This approach provides a mechanism for stating the prescription exactly without variation. For example, institutions can be instructed to normalize a treatment plan so that exactly 60 Gy is delivered to cover 95% of the PTV. All institutions would be expected to be able to follow this instruction. However, the prescription has to be more

extensive than the simple sentence given above in order to accommodate the dose variation within and around the PTV that will result as many different institutions plan different patients.

## **Recommended Prescription Method for RTOG Protocols**

### *Sequential boost technique*

The RTOG uses a volume prescription technique for 3D-CRT and IMRT treatments. The technique is designed to guarantee that the prescribed dose covers the PTV without extending unnecessarily outside of this volume. Thus, somewhat less than 100% coverage of the PTV is stated to constrain the dose. Some variation in the level of coverage is allowed from protocol to protocol, but not within a particular protocol. As an example, a typical protocol might state that dose will be normalized such that 95% of the PTV is covered by the stated prescribed dose. This level of coverage is used to provide for treatment sites where one or more critical structure pushes against or invaginates (creates a concavity in the volume) the surface of the PTV. For treatment sites where sensitive critical structures do not encroach on the PTV, it is more common to use 98% coverage of the PTV for stating prescription dose. Adding the words “at least” in front of this number is not an acceptable way of stating the dose prescription for RTOG protocols. Also, using 100% is not allowed because this statement can encourage the use of oversized fields to provide PTV coverage.

Writing the prescription with either 95 or 98% coverage of the PTV has the disadvantage of underdosing part of the PTV. This is not a major problem given the penumbra falloff for a single beam of radiation and the even slower dose decrease that results when multiple field treatment plans are employed. However, in order to bring attention to this potential problem, RTOG prescriptions include a statement of the minimum dose that is allowed within the PTV. In order to avoid the reporting of artifacts that can occur within the dose distribution, this dose value is stated along with the volume of the point for determining this dose. For example, the minimum dose might be stated as being greater than or equal to 97% of the prescribed dose for a volume that is at least 0.03 cc (approximately 3x3x3 mm) in size. That is, this statement guarantees that the lowest dose for such a small volume within the PTV cannot fall below 97% of the prescribed dose. The maximum dose within the PTV is also included as part of the RTOG prescription. The same format used for the statement of the minimum dose is used for describing the maximum dose. A typical dose level for the maximum dose for IMRT treatments is 110% of the prescribed dose for a small point within the PTV that is a least 0.03 cc in size. Thus, the statement when this limit is used would be that the maximum dose must be less than or equal to 110% of the prescribed dose.

Other dose values used for RTOG prescriptions are the maximum allowed dose occurring outside of the PTV and the dose for particular critical structures. Critical structure dose limits should include at least two points. Typically, the maximum dose plus one other point on the anticipated DVH curve is stated as part of the prescription. The maximum dose values are again stated for a small volume of 0.03 cc.

## Technique Examples:

The **IMRT** prescription for the RTOG 0724 protocol titled “PHASE III RANDOMIZED STUDY OF CONCURRENT CHEMOTHERAPY AND PELVIC RADIATION THERAPY WITH OR WITHOUT ADJUVANT CHEMOTHERAPY IN HIGH-RISK PATIENTS WITH EARLY-STAGE CERVICAL CARCINOMA FOLLOWING RADICAL HYSTERECTOMY”:

The vaginal planning target volume (PTV) (ITV with 7.0 mm margin) and nodal PTV will receive either 45 Gy in 25 fractions or 50.4 Gy in 28 fractions. Treatment will be delivered once daily, 5 fractions per week, over 5 to 5.5 weeks. All targets will be treated simultaneously with the same dose.

The dose is prescribed to cover 97% of the vaginal PTV and nodal PTV. A volume of at least 0.03 cc within any PTV should not receive > 110% of the prescribed dose. No volume within the PTV that is 0.03 cc or larger can receive a dose that is < 93% of its prescribed dose. Any contiguous volume of 0.03 cc or larger of the tissue outside the PTVs must not receive > 110% of the dose prescribed to the primary PTV.

Bowel: 30% to receive  $\leq$  40 Gy. No volume within bowel that is 0.03 cc or larger receives a dose that is greater than prescription dose.

Rectum: 60% to receive  $\leq$  40 Gy. No volume within rectum that is 0.03 cc or larger receives a dose that is greater than prescription dose.

Bladder: 35% to receive  $\leq$  45 Gy. No volume within bladder that is 0.03 cc or larger receives a dose that is greater than prescription dose.

Kidneys: 2/3 of each kidney to receive  $\leq$  18 Gy

Spinal cord: no more than 45 Gy at any point with a volume of 0.03 cc or greater

### *Compliance Criteria*

The compliance criteria are written to extend some aspects of the prescription. As stated above, institutions are expected to be able to normalize treatment plans to meet the stated percentage of PTV coverage by the prescribed dose. Therefore, the compliance criteria given in the protocol do not allow variation in this part of the prescription statement. Variations in other parts of the prescription are allowed. This applies to the maximum, and minimum dose limits for both the PTV and critical structures. Other points on the expected DVH curves for both the PTV and critical structures can be extended as part of the compliance criteria.

Returning to the example of the 0724 protocol for the IMRT stratification, the compliance criteria are reproduced here for the *variation acceptable* dose limits for the PTV. These limits are:

The 0.03 cc volume of overdose for the PTV exceeds 110% of the prescribed dose but remains at or below 115%.

The variation acceptable compliance criteria for critical structures for the 0724 protocol are as follows:

Bowel: variation acceptable 30% to receive  $> 40$  Gy but  $\leq 45$  Gy  
Rectum: 60% to receive  $>40$ Gy but  $\leq 45$ Gy  
Bladder: variation acceptable 35% to receive  $> 45$  but  $\leq 50$  Gy

A volume of at least 0.03 cc of any critical structure exceeds 110% of the prescribed dose but remains at or below 115% (except for spinal cord for which the maximum limit at any point is set at  $\leq 45$  Gy)

### **Sequential Boost Technique**

Sequential boost techniques are usually accomplished by applying the same prescription techniques described above for each cone-down treatment. Composite treatment plans are required for most RTOG protocols.

### **Combined Boost Technique**

When different doses are required to treat regions with different risk, a combined boost treatment is commonly used for IMRT dose delivery where all prescription levels are optimized together. The example of a combined boost treatment is RTOG protocol #0522 titled “A RANDOMIZED PHASE III TRIAL OF CONCURRENT ACCELERATED RADIATION AND CISPLATIN VERSUS CONCURRENT ACCELERATED RADIATION, CISPLATIN, AND CETUXIMAB (C225) FOR STAGE III AND IV HEAD AND NECK CARCINOMAS.” The dose prescription for this protocol is reproduced below:

IMRT will be given in 35 fractions over 6 weeks, which requires delivery of 6 fractions per week during 5 of the 6 treatment weeks. The sixth fraction can be delivered either on Saturday or as a second daily fraction, with at least a six-hour interfraction interval, on one of the weekdays. The primary tumor and involved nodes (PTV<sub>HD</sub>) will receive 2 Gy per fractions and subclinical disease sites (PTV<sub>ED</sub>) will receive 1.6 Gy per fraction. The total doses will thus be 70 Gy and 56 Gy, respectively.

The specific statement for the PTV<sub>HD</sub> and the critical structure doses is as follows:

All plans must be normalized such that 95% of the volume of the PTV<sub>HD</sub> is covered with the prescription dose of 70Gy.

Additionally:

- No more than 20% of the PTV<sub>HD</sub> should receive  $\geq 110\%$  of the prescribed dose;
- No more than 1% of any PTV<sub>HD</sub> or PTV<sub>ED</sub> should receive  $\leq 93\%$  of the prescribed dose;
- No more than 1% or 1 cc of the tissue outside the PTVs should receive  $\geq 110\%$  of the prescribed dose to the PTV<sub>HD</sub>.

The dose limits for the critical structures for this protocol are:

*Spinal cord:* A margin of 0.5-1cm around the spinal cord may be added to create a Planning Organ at Risk Volume (PRV). The dose to any point within the spinal cord should not exceed 48 Gy to any volume larger than 0.03 cc (approximately equivalent to a 3x3x3 mm cube).

*Parotid glands:* When using IMRT, the objective is to limit the mean dose to at least one gland to  $\leq 26$  Gy; alternatively at least 20 cc of the combined volume of both parotid glands to  $< 20$  Gy or at least 50% of one gland to  $< 30$  Gy.

*Glottic larynx:* In patients with oropharyngeal carcinoma without extension to the larynx, placing the isocenter just above the arytenoids and irradiating the lower neck with an anterior matching field with larynx block can minimize the dose to the glottic larynx. Alternatively, the dose to the larynx should be kept  $< 45$  Gy whenever feasible.

*Brachial plexus:* The dose to the brachial plexus must be limited to  $\leq 60$  Gy in patients with level IV node(s).

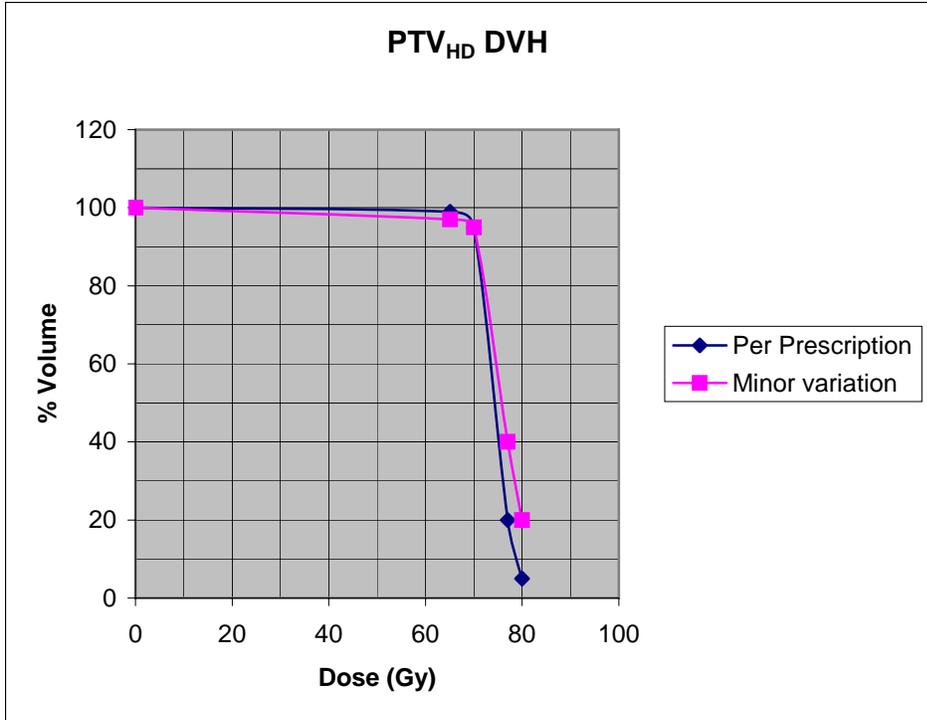
*Unspecified tissue outside the target volumes:*  $\leq 100\%$  of the dose prescribed to CTV1. No more than 5% of the non-target tissue can receive greater than the dose to CTV1.

For the PTV<sub>HD</sub> for this protocol, an ideal DVH is a step function that drops precipitously at the prescribed dose of 70 Gy. Obviously, due to beam and treatment planning limitations, this ideal DVH is not achievable. The statement of the prescription takes this into account by providing a shoulder and tail to the ideal DVH. The RTOG #0522 protocol includes a figure to illustrate the DVH the institution is expected to provide. This figure is copied from the protocol and copied below. Referring to this figure, the institution is encouraged to obtain a plan with a DVH that falls between the ideal step function and the blue curve with diamond symbols. The statement that the institution must as a guide for treatment planning is as follows:

A region of “variation acceptable” is also defined in the figure as the DVH represented by the square symbols. Deviations of this magnitude are not desirable, but will be deemed acceptable. That is, a DVH with at least 97% of the volume receiving 65 Gy is allowed as a variation acceptable. Additionally, as a variation acceptable for the overdose region, as much as 40% of the PTV<sub>HD</sub> volume can receive 77 Gy and up to 20% of this volume can receive 80 Gy. DVHs for the PTV<sub>HD</sub> falling outside the limits for a variation acceptable (i.e., increased under or overdose) will be scored as a “deviation unacceptable.”

The 0522 protocol specifically define the deviation unacceptable as follows:

DVHs for the PTV<sub>HD</sub> falling outside the limits for a violation acceptable (i.e., increased under or overdose) will be scored as a “deviation unacceptable.”



Dose (Gy)	Per Protocol	Variation Acceptable
65	99%	97%
70	95%	95%
77	20%	40%
80	5%	20%