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Introduction and Clinical Overview of the DVH Risk Map

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Radiation oncologists need reliable estimates of risk for various fractionation schemes for all critical anatomical structures throughout the body, in a clinically convenient format. Reliable estimation theory can become fairly complex, however, and estimates of risk continue to evolve as the literature matures. To navigate through this efficiently, a dose-volume histogram (DVH) Risk Map was created, which provides a comparison of radiation tolerance limits as a function of dose, fractionation, volume, and risk level. The graphical portion of the DVH Risk Map helps clinicians to easily visualize the trends, whereas the tabular portion provides quantitative precision for clinical implementation. The DVH Risk Map for rib tolerance from stereotactic ablative body radiotherapy (SABR) and stereotactic body radiation therapy (SBRT) is used as an example in this overview; the 5% and 50% risk levels for 1-5 fractions for 5 different volumes are given. Other articles throughout this issue of Seminars in Radiation Oncology present analysis of new clinical datasets including the DVH Risk Maps for other anatomical structures throughout the body.
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Human dose tolerance to conventionally fractionated radiation has been analyzed for many decades. The development of isoeffect curves,[1] nominal standard dose,[2] and time dose fractionation tables[3] eventually led to biological effective dose (BED)[4] based on the linear quadratic (LQ) model,[5-9] and many other models for biological equivalence continue to be investigated.[10-17] Dose-response modeling[18-29] provides a more explicit way to estimate the actual risk levels for each critical anatomical structure as a function of dose, fractionation, volume, and other parameters.

The work of Emami et al[30] combined this theoretical framework with clinically usable dose-tolerance limits like Rubin[31-34] to provide 5% and 50% risk levels for 25 anatomical structures throughout the body. After 10 years, the July 2001 issue of Seminars in Radiation Oncology[35] presented a comprehensive update of the modeling results, and after about another 10 years, most of the lead authors from that work became authors of Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC),[36] which is currently the most accurate assessment of normal tissue complication probability (NTCP) for conventional fractionation.

Dose tolerance for stereotactic ablative body radiotherapy and stereotactic body radiation therapy (SBRT) is still much more uncertain. The authors began delivering CyberKnife treatments before most of the Radiation Therapy Oncology Group stereotactic ablative body radiotherapy (SABR) or SBRT protocols,[37-40] before the report of American Association of Physicists in Medicine Task Group 101 (TG 101),[41] before QUANTEC,[36] and before the Timmerman 2008 issue of Seminars in Radiation Oncology.[42] Dose-tolerance guidelines were extremely rare, and we began accumulating a simple spreadsheet of the sparsely published data. Over time, it grew to 500 dose-tolerance limits[43] and as of 2016, there are well over 1000 published limits—but they are discordant, ever changing, and until now have lacked quantitative estimates of corresponding incidence of complication.

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Dose-Tolerance Limits Defined

Much has been said about dose-tolerance limits, but our formal definition may clarify:

Dose-Tolerance Limit

A specified radiation dose, fractionation, and volume, with an associated estimated risk of developing a complication of a specified endpoint within a specified follow-up time.

Human dose tolerance to radiation depends on many other factors, but a well-defined dose-tolerance limit must specify at least the following:

(1) Dose
(2) Fractionation
(3) Volume
(4) Endpoint
(5) Follow-up time
(6) Estimated risk of the endpoint occurring within the follow-up time

The endpoint and length of follow-up must be clearly stated in order for the dose-tolerance limit to be useful. Emami used 5 years as the follow-up period for every dose-tolerance limit, and although this is convenient, there is not much 5-year quantitative data available yet in the SBRT literature. Note that a 5-year follow-up period implicitly includes both early and late effects, but for SBRT in particular, there is much interest in distinguishing the timing of the onset of symptoms.

Finally, for a dose-tolerance limit to truly be useful in clinical decision making, it must include an estimate of the associated risk of the endpoint occurring within the specified time. The circumstances of each patient and each tumor are unique. We need reliable estimates of complication probability which would provide physicians with the information needed to make the most informed decisions.

Simple Graphs and Physical Dose

If the information relating a range of dose-tolerance limits and their respective risks could be arranged on a single graph it would help physicians make decisions about management. In an attempt to make sense of contradictory published SBRT constraints, simple graphs of the dose-tolerance limits as a function of the number of fractions were made, which led to the creation of the dose-volume histogram (DVH) Risk Map.[44] Initially, our tendency was to perform a BED conversion of the doses before plotting them. We quickly realized, however, that currently the BED conversions themselves were just one more confounding factor that made comparisons more difficult, as there are so many methods of BED conversion.[4-17] Owing to the lack of thorough reporting standards,[45] it has often not been feasible to unravel the conversions of one publication and recompute to the conversions of another.

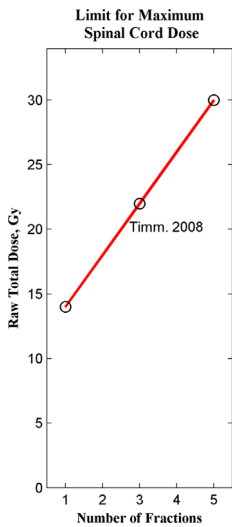
Therefore, we tried simply plotting the dose-tolerance limits on a linear scale; pure physical dose. Much to our surprise, we discovered that someone else must have already come to this realization, because as may be clearly seen by plotting the limits as in Figure 1, many of the Timmerman 2008 limits are related by straight lines. It is not possible to express what a profound influence these few straight lines have had on the field of radiation oncology in SBRT—they may be simple, but they have been a remarkably useful starting point. Furthermore, the potential linearization of BED at high dose per fraction as expressed in the universal survival curve (USC)[15] does provide a plausible theoretical justification, although, as with all BED conversions, there is some debate.[16,17]

The USC is one of many models that have been proposed as alternatives to the LQ model for biological equivalence, including linear quadratic cubic (LQC),[14] linear quadratic linear (LQL)[10-12] and others.[13,17]

In the DVH Risk Map graphs, dose is on the y-axis, each subplot is for a specific volume, and the number of fractions is on the x-axis of each subplot. There are many dose-volume metrics that combine dose and volume together, such as the inverse power law,[24] effective volume (V_{eff}),[46] effective dose (D_{eff}),[47] or equivalent uniform dose (EUD).[48] Any of these metrics can be used to specify a dose-tolerance limit, and any of these can be used as one of the 5 subplots in a DVH Risk Map.

Low-Risk and High-Risk Partition

Every patient is unique, especially considering the variability of tumors and the proximity to critical structures, so a range of dose-tolerance limits is needed. Over a period of more than 20 years, Rubin[31-34] and Emami[30,26] determined a unified format of low-risk and high-risk dose-tolerance limits for



Num. of Fract.	Dmax Limit (Gy)
1 fx	**14.0**
3 fx	**22.0**
5 fx	**30.0**

Figure 1 Simplified DVH Risk Map for spinal cord, for maximum point dose (D_{max}) limits in 1, 3, and 5 fractions from Timmerman 2008, with a straight line interpolation from 1-5 fractions. The universal survival curve (USC)[15] is linear at high dose per fraction. (Color version of figure is available online.)