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Three-dimensional radiation therapy (RT) planning tools provide detailed information regarding the degree of radiation exposure to different volumes of organs. Presently, we have incomplete knowledge regarding the tolerance doses for different normal tissue organs. The classic "Emami paper" (IJROBP 1991) provided broad dose/volume guidelines for 3D RT planning, based on somewhat limited clinical data. More recently, there has been dramatic increase in the number and quality of clinical studies that attempt to relate dose/volume parameters to normal tissue risks. Presently, dosimetric parameters predictive for injury are available for several organs (e.g. the lung, heart, esophagus, parotid, and brain), and additional/better data is rapidly accumulating. However, for most organs, the presently-available predictive models are suboptimal. The continued challenges include: non-uniform definitions of toxicity (e.g. radiologic vs. analytic vs. symptomatic), clinical comorbidities that make the diagnosis of RT-induced toxicity uncertain, the confounding effects of concurrent chemotherapy (that is being used with increasing frequency), and multi-organ nature of some clinical endpoints. Further, it is not clear if the dose/volume guidelines developed in the "3D era" are applicable in the hypofractionated/radiosurgery/IMRT era. Extreme caution is warranted to the extrapolation of dose/volume guidelines beyond the scope within which they were defined. For example, the variable fraction size delivered to the surrounding normal tissues with IMRT/radiosurgery is fundamentally different than the relatively-uniform fraction sizes received by the normal tissues in the 3D era. Since most normal tissue effects are very sensitive to fraction size, this variable needs to be considered. IMRT actually makes the decision-making process more complex for the physician, as we now have greater flexibility regarding where to deposit the "extraneous/incidental" RT dose. Thus, the need for better dose/volume guidelines, that include consideration of fraction size, has increased with IMRT. When normal tissue dose/volume data becomes more robust, we will be better able to exploit the full potential of 3D/IMRT to minimize radiation-induced normal tissue injury.