The Impact of IGRT on Normal Tissue Toxicity

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Abstract

Image Guided Radiation Therapy (IGRT) deploys advanced imaging techniques prior to each treatment to ensure the highest possible agreement between the planned treatment geometry and the daily set-up. This agreement includes both the patient position and the localization of the internal target and normal structures. This process reduces non-tumor tissues within the target volume to a minimum. IGRT is now commonly accompanied by altered fractionation schemes, usually hypofractionation. With the small-volume, high-dose-per-fraction treatments, the profile of treatment morbidities may change, compared to conventional 3D treatment. This chapter explores how these morbidities may change with the use of IGRT.

Keywords

Image guided radiation therapy · Normal tissue toxicity

1 Introduction

Technological advances in radiation oncology have largely focused on delivering as much dose as possible to the target volume while minimizing normal tissue (NT) morbidity.[1] This has been accomplished by deploying increasingly complex

[1]Only recently has de-escalation of target dose become a serious line of investigation in radiation oncology.

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field arrangements of increasingly smaller beamlets and arcs and by using immobilization and imaging to ensure proper patient positioning and targeting of the planning target volume.[2] The result has been sharper dose gradients at the margin of the high dose region and lower doses to normal tissues. If no change is made in the dose per fraction or in the total tumor dose, then normal tissue toxicity will necessarily be reduced because normal tissue doses are reduced. However, as technology has improved, tumor doses have been escalated, generally (or at least initially) by increasing the number of fractions rather than the dose per fraction. Under the assumption that as tumor doses increase, the same dose limits on normal tissue are respected, then the NT dose per fraction will decrease, again decreasing the morbidity. Thus it is self-evident that deploying IGRT either while keeping target doses the same, or while increasing them but keeping NT tissue doses the same will decrease NT morbidity if the target dose per fraction is held constant or will hold NT morbidity constant if the target dose per fraction is increased. The exception to this statement is the morbidity to normal tissues within the target volume itself.

We will explore three scenarios where a tradeoff occurs between local control and NT morbidity when IGRT replaces conventional treatments. We investigate these scenarios primarily with respect to the changes in NT morbidity. Some increase in local control will be assumed so that dose escalation may be justified, but it is the potential increase in NT morbidity that will be explored in order to determine how much the target dose may be safely increased.

The first scenario is the use of IGRT to escalate target dose with conventional fractionation where the NT doses are also increased but the NT dose per fraction decreases. To explore this scenario requires knowledge of the fractionation effects on normal tissues. The volume effects will not greatly impact the morbidity in this case since the relative dose distribution would not be expected to change dramatically.

The second scenario is the use of IGRT to escalate the effective target dose by deploying hypofractionation in addition to IGRT. This technique is often limited to small volume treatments, with a concomitant small volume of irradiated NT. In this situation, the volume effect can be paramount and may even result in the nature of the NT morbidity being different from what would typically be observed when large NT organ volumes are irradiated.

Finally, the third scenario is the use of single fraction IGRT, which can be considered as the limit of hypofractionated IGRT. The tissue at risk in this scenario is very commonly nervous tissue.

The radiobiological considerations in these three scenarios may be different and will be discussed separately.

[2]In this chapter, IGRT will be assumed to include daily volumetric imaging prior to treatment. Early definitions of IGRT included multimodality imaging to define better the target volume. In this chapter, we will consider only the impact of daily imaging on NT responses. In IGRT like in quantum mechanics, we assume you know where something is only when you look for it.

2 Radiobiological Foundations

2.1 A Brief History

IGRT highlights the longstanding discussion regarding the relative importance of dose versus volume in radiation induced normal tissue toxicity. The specific issue is whether toxicity is more sensitive to changes in irradiated volume at a constant dose or changes in dose at a constant volume. Historically, most technical improvements in radiation dose delivery (custom blocking, CT simulation, conformal therapy, IMRT, IGRT, adaptive treatment) have been claimed to have the potential to increase the tumor dose (local control) and/or decrease normal tissue doses/volumes (morbidity) by improving the targeting of the radiation treatment. In the 1970s and 1980s, the same objective was attempted by manipulating the fractionation schedule using split course treatments and searching for the best dose per fraction whether deployed in conventional, hypofractionation, or hyperfractionation schedules. These efforts met with limited success, but the emphasis on "tighter" dose distributions and better definition of treatment objectives as exemplified by the publication ICRU 50 ultimately led to greater success (IRCU 50, 1993). The proof-of-principle study in controlling dose distributions was RTOG 94-06, A Phase I/II Dose Escalation Study Using Three Dimensional Conformal Radiation Therapy for Adenocarcinoma of the Prostate(Michalski et al. 2000). The genesis of this RTOG study was an NCI-sponsored cooperative study "National Collaborative Radiation Therapy Trials: 3-D Dose Escalation Study for Prostate Cancer." Rapid advances in delivery technology and 3D dose calculations made it possible to transition from the introduction of conformal radiation therapy in the mid 1990s to IGRT with helical tomotherapy in less than 10 years. IGRT using arc therapy on C-arm linacs followed rapidly thereafter.

2.2 Some Biological Considerations

How NT morbidity changes with changes in dose and volume depends upon how the tissue is organized morphologically and the pathogenesis of the injury. A useful concept used in discussing NT morbidity is the functional subunit, FSU, first introduced in radiation oncology by Withers et al. (1988). The FSU is a construct to model how the organ or tissue is organized, but in some cases the idea has been carried beyond its connection to reality. Withers et al. argued that FSUs could be organized either in parallel, when the loss of some FSU's would not necessary result in a radiation injury, or in series where the loss of a single FSU would yield an injury. In the former case, FSU's organized in parallel is a tautology. If an organ has FSU's, logic demands that they are organized in parallel. Those organs that have functional reserve can be said to have FSU's. In those organs, part of the organ can be lost and the remainder of the organ can fulfill its function. The lung, kidneys, and liver are some obvious examples. However, if an organ fails when a single component fails,

then the entire organ functions as a single unit and there are no *sub*units. If there is no functional reserve, that is, if no part of the organ accomplishes a portion of the task of the organ as a whole, then there is a single functional unit.

In radiation response, not just the tissue organization, but the pathogenesis is relevant to the determination of FSU's. Veno-oclusive disease is a potential radiation injury, but it is fundamentally a complication of the whole liver (Klaus Trott, personal communication). Radiation induced liver disease, formerly known as radiation hepatitis, is a complication that manifests at higher doses to a fractional portion of the liver(Dawson et al. 2002; Lawrence et al. 1995). Thus a single organ may have different FSU's depending on the injury type.

The spinal cord is generally held to be the paradigm of an organ made of serial functional subunits. However, the fundamental function of the spinal cord is to transmit reliably a signal from the brain to a remote tissue or vice versa. If part of the spinal cord is damaged, the signal is not reduced, it is interrupted. The spinal cord acts as one, single electrical cable.

The confusion that led to the erroneous concept that organs without subunits have serial architecture probably had its genesis in the fact that the original version of the critical element model (a volume effects model) assumed a complication was the result of a lesion of sufficient size occurring anywhere in the organ it risk, as in the spinal cord (Schultheiss et al. 1983). The probability of a lesion occurring in a fractional volume, v, of uniformly irradiated tissue was estimated by

$$P(D, v) = 1-(1 - P(D, 1))^{v}$$

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where P(D, 1) is the probability of a lesion occurring if the entire organ is irradiated to dose D. This formula was derived using the simple notion that the probability of a lesion *not* occurring in the organ was the product of the probabilities of its not occurring in all subvolumes of the organ. This model is easily generalized to an inhomogeneous dose distribution, and it has the advantage that the probability of complication is based on the dose response function of a uniformly irradiated whole organ, the most likely form that clinical data of that era would take. However, the mathematical "trick" of using subvolumes does not imply the existence of FSU's.

Jackson and colleagues developed a similar model for organs with actual FSU's (Jackson and Kutcher 1993; Jackson et al. 1995). Rather than the production of a single lesion, they modeled a volume *element* as having suffered a binary level of damage. The endpoint was reached if a sufficient number of volume elements, presumed to be FSU's, suffered damage. Unfortunately, this formalism requires the dose response function for the FSU in order to determine the organ response. It is not possible to determine the dose response function of a partially irradiated organ based on the dose response of the whole organ. One can see how the division of a so-called serial organ encouraged the mistaken association of these volume elements with FSU's, as they truly are in an organ with functional reserve.

Both the critical element model and the parallel architecture model are examples of what is known in reliability systems as a k-out-of-N system; the system fails if k

of the N elements of the system fail, and is denoted as a k-out-of-N:F. The critical element model is a 1-out-of-N:F system and the parallel model is a k-out-of-N system. A k-out-of-N:G system is good (G) if k of the component remain functional. There are consecutive k-out-of-N systems where a linear system fails if k *consecutive* components fail. The critical element or serial model is a k-out-of-N system with $k = 1$. The parallel architecture model of Jackson et al. is a nonconsecutive k-out-of-N system, where N is the number of FSU's and k is the number that must fail to elicit a radiation complication. Tumors are typically modeled as k-out-of-N:G systems with $k = 1$. That is, as long as a single clonogen is good, the tumor is viable. More complex models can be made by adding higher dimensions, i.e. two and three dimensional k-out-of-N systems. However, consecutive k-out-of-N systems are mathematically very complex (or at least tedious), and higher dimensional systems have the disadvantage of being simultaneously nearly intractable while having too many independent variates in the model to be statistically useful for modeling normal tissue responses.

3 Fractionation Scenarios

3.1 Conventionally Fractionated Treatments

Image guidance today is primarily achieved with commercially available on-board systems used for daily volumetric imaging in radiation therapy setups such as cone beam CT and megavoltage CT. Open MRI coupled with rotational Co-60 beams has been developed recently and ultrasound imaging is still commercially available. Early versions of daily CT scanning involved scanning on a CT simulator prior to treatment and transferring the patient to a treatment table using a transfer board (Lattanzi et al. 1998). The authors concluded, "With daily isocenter correction of setup and organ motion errors by CT imaging, PTV margins can be significantly reduced or eliminated. We believe this will facilitate further dose escalation in high-risk patients with minimal risk of increased morbidity." This technique was compared to the use of transabdominal ultrasound in the treatment position for prostate cancer (Lattanzi et al. 1999). The two were found to be "functionally equivalent."

Thus even as conformal therapy was transitioning to IMRT in the 1990s, efforts to deploy IGRT were already being made. Outside of SRS treatments, these initial efforts were primarily focused on reducing the CTV-PTV margin by reducing set-up variations and imaging the target volume every day. The objective was to increase tumor dose without increasing morbidity. Megavoltage CT was being deployed with a prototype helical tomotherapy for the same purpose (Mackie et al. 1995; Yang et al. 1997). In-room CT was also deployed later with varying success (Owen et al. 2009).

In an extensive study of set-up variations versus the frequency of imaging in IGRT, Han et al. determined the likelihood of a decrease in coverage of the target

volume and an increase in NT irradiated volumes when imaging occurred at frequencies of 0, 20, 40, and 60% versus daily (100%) imaging (Han et al. 2012). Even at an imaging frequency of 60%, the lung volume receiving 0.8 Gy per day and the heart volume receiving 1.2 Gy per day increased by more than 20% in 10% of the fractions. The CTV receiving 95% of the daily dose (1.8 Gy) decreased by more than 20% in 5% of the fractions. This is primary evidence that by deploying daily image guidance, the NT doses can be decreased and target doses increased. Complications rates and the types of side effects would not change. Conversely, if the target dose did not change, complication rates could decrease without affecting the types of complications. This was observed by Chung et al. in prostate cancer (Chung et al. 2009).

It is important not to overstate the effect of image guidance. Clearly, an advantage is seen since the NT DVH is shifted to lower doses (and the PTV DVH becomes steeper). However, it is important to acknowledge that part of this shift is a result of reduced margins afforded by daily imaging (IGRT) and part results from improved dose fall-off away from the target due to improved dose *delivery* technology (IMRT). It is difficult to find in the literature clinical studies that compare similar IMRT techniques with dissimilar imaging protocols. It is the imaging that distinguishes IGRT from IMRT.

3.2 Hypofractionated Treatment

The failure of early hypofractionation resulted from a lack of understanding of radiobiology and the response of normal tissues to radiation. It was believed, or more accurately hoped that morbidity from increases in daily doses could be offset by lengthening the interfraction interval. Furthermore, the biological consequence of increasing the dose per fraction was underestimated. Unfortunately these early attempts were undertaken when field shaping was unsophisticated, volume effects were underestimated, and treatments were frequently delivered using one field per day. By the late 1980s, hypofractionation, often combined with split course treatments, was largely abandoned in the definitive setting (Overgaard et al. 1988; Parsons et al. 1980). Late complications, which are more sensitive to changes in dose per fraction than tumors, increased without a compensating increase in tumor control because the relative dose distributions were not altered.

By sparing normal tissues, IGRT reduces both the dose per fraction and the volume of NT irradiated without reducing the tumor dose. Increasing the dose per fraction to the tumor so that the NT dose per fraction remains approximately constant would still leave a smaller volume of NT irradiated. Using hypofractionation, investigators have tested the hypothesis the NT morbidity will not increase because reduced irradiated volumes will compensate for any increase in dose per fraction. The truth to this hypothesis largely rests on the nature of the volume effect and the pathogenesis of the NT morbidity.

As discussed above, prostate cancer was among the sites where IGRT was deployed early in its history, initially with conventional fractionation. Because

doses were being escalated to 80 Gy and higher, overall treatment times were extending beyond 8 weeks. In part to shorten the overall duration of treatment, hypofractionation trials were initiated. In general, the GI late toxicities are similar into those seen with the best conformal or IMRT results. However, there is a strong tendency to report slightly greater GU toxicity in IGRT than in conformal treatments, although severe late GU toxicity is rare.

Rectal toxicity generally includes symptoms of radiation proctitis (urgency, frequency, mucus discharge, pain) or rectal bleeding. Rectal bleeding would not be expected to be very volume dependent, but to depend rather more on dose; however, Wu et al. reported no rectal bleeding in 72 patients treated with a schedule of 16 × 3.4 Gy (Wu et al. 2012). In this report, as in several others (King et al. 2009; Madsen et al. 2007; Pollack et al. 2013), GU toxicity was a greater problem than GI toxicity.

The relatively greater incidence of GU toxicity in IGRT for the prostate can be reasonably explained by the fact that the urethra is in the high dose volume whereas the rectum can largely be excluded from the target volume. Obviously as the target dose is escalated, so are the doses to most GU tissues that are at risk for radiation injury.

A somewhat similar effect occurs in the lung. The relative frequency of toxicity changes in two ways when conformal fields shrink to SBRT fields with the concomitant increase in dose per fraction (Kollar and Rengan 2014). As seen in animal models (Van Der Veen et al. 2016), there is a shift from early to late effects as the volume is reduced. Furthermore, at the higher doses per fraction, the central normal structures become more likely to express morbidity than peripheral lung parenchyma. These effects are independent of yet a third possibility–spatial variation in lung sensitivity as seen in mouse models and attributed to the spatial variation in target structure for radiation pneumonitis (Tucker et al. 1997).

In the CNS, both brain and spinal cord, there appear to be no changes in the types of normal tissue morbidity that result from reducing volumes and number of fractions while increasing the dose per fraction. The obvious exception is that neurocognitive deficits result from large volume treatment of CNS. However, one must still be cognizant of differing sensitivity of different regions. For example, there is some evidence that thoracic spinal cord is less sensitive than the cervical cord. The lumbar cord is also less sensitive, possibly owing to its being myelinated with Schwann cells rather than oligodendrocytes.

In addition to dose and volume factors associated with normal tissue responses in changing from conventional fractionation and target volumes to hypofractionation and image guided target volumes, different biological factors and responses may come into play at larger doses per fraction. With higher biological doses that result from higher doses per fraction, not only are direct effects observed, but the microenvironment in the target region is altered by release of inflammatory mediators and molecular factors that may alter vascular permeability, induce changes in fibroblasts, and impact the endothelial cell compartment (Song et al. 2014; Zeng et al. 2014). Research has concentrated on the impact of these effects on tumor

response and tumor growth, but the impact on normal structures inside the IGRT target volume has received relatively little attention.

3.3 Single Fraction Treatments

Reoxygenation, redistribution or reassortment, repair, and repopulation comprise the 4 R's of radiotherapy. Reoxygenation is probably irrelevant to normal tissue and repopulation is not very important in late injury. Clearly reassortment and repair are not factors if single fraction treatments are used. Thus single fraction treatments cannot benefit from the traditional advantages of fractionation, which generally reduce normal tissue injury while simultaneously enhancing tumor sensitivity. Of course there are many examples of failed single-fraction efforts in the history of radiation oncology. The success of single fraction IGRT can be largely attributed to the significant geometrical advances of IGRT and the fact that we have learned the cost of treating large volumes using single fractions.

There may some biological advantages to single fractions as described elsewhere in this volume. See *Optimizing radiation dose and fractionation* in the Chapter "Advances in Immunotherapy." However, it seems any putative advantages would not outweigh the advantages of fractionation. High-dose radiation treatments may impact tumor control through stromal effects not predicted by classical radiobiological considerations (Brown et al. 2014; Hellevik and Martinez-Zubiaurre 2014). However, these stromal effects are not dependent on the radiation being given in a single fraction.

One might be tempted to believe that the probability of a geographic miss would increase with fractionation. However, the probability of a miss is the same if equal care is given to N fractions in a single patient or in single fractions to N patients.

Thus from biological and physical arguments, fractionated treatment still appears to be advantageous. The advantage of single fraction treatments comes primarily in patient convenience and especially for palliative cases (Greco et al. 2011).

4 Conclusions

The emphasis of this chapter is not to list the normal tissue complications observed in IGRT. It is to describe how morbidity profile and pathogenesis might change in going from conventional treatments to image guided treatments. In deploying image guided treatments, effective doses are generally escalated, dose per fraction increases, and volumes are decreased. If the tumor dose is increased solely by increasing the number of fractions as was done in the early days of IGRT for prostate cancer, then the character of the morbidities is unlikely to change although the relative frequency might as a result of increased morbidity to the normal tissues in the target volumes and decreases elsewhere.

Hypofractionation and single fraction IGRT are almost always associated with small-target-volume treatment. The small target volumes can result in significant changes in the normal tissues at risk, the types of morbidities elicited, and a shift from early to late effects. When using high doses per fraction, the likelihood increases that the morbidity will be associated with local necrosis and late fibrosis. Combining high doses per fraction and small volumes can result in morbidities rarely seen in conventional treatments, such as those seen in central lung structures after SBRT.

There seems to be little to recommend single fraction treatments over hypofractionation. In nearly all cases, the biology for normal tissue recovery and tumor cell kill seems to favor some fractionation. The statistics of treatment set up do not favor single fraction treatments. Patient convenience is the only measure in which single fraction treatments have an advantage. This may be important in palliative cases, if a cogent argument for image guided treatment can be made in the palliative setting.

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