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ACCURATE ACCUMULATION OF DOSE FOR IMPROVED UNDERSTANDING OF RADIATION EFFECTS IN NORMAL TISSUE

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Abstract

The actual distribution of radiation dose accumulated in normal tissues over the complete course of radiation therapy is, in general, poorly quantified. Differences in the patient anatomy between planning and treatment can occur gradually (*e.g.*, tumor regression, resolution of edema) or relatively rapidly (*e.g.*, bladder filling, breathing motion) and these undermine the accuracy of the planned dose distribution. Current efforts to maximize the therapeutic ratio require models that relate the true accumulated dose to clinical outcome. The needed accuracy can only be achieved through the development of robust methods that track the accumulation of dose within the various tissues in the body. Specific needs include the development of segmentation methods, tissue-mapping algorithms, uncertainty estimation, optimal schedules for image-based monitoring, and the development of informatics tools to support subsequent analysis. These developments will not only improve radiation outcomes modeling but will address the technical demands of the adaptive radiotherapy paradigm. The next 5 years need to see academia and industry bring these tools into the hands of the clinician and the clinical scientist.

Keywords

Dose accumulation; Normal tissue effects; Deformation; Four-dimensional; Informatics

THE DOSE DELIVERED

Continued advances in clinical practice demonstrate that there is more work to be done both in terms of the accuracy of dose computation methods and the accurate accumulation of

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dose in the dynamic anatomy of the human body. In addition to reducing the volume irradiated to therapeutic levels, imaging and targeting technologies are highlighting the dynamic nature of patient anatomy over the course of therapy (1, 2). Leaving aside the difficulty of mapping tumor regression, investigators have established the potential to estimate the "true dose" or D_A to any volume of normal tissue applied over the course of therapy (3, 4) with numerous studies demonstrating the degree of dose variation that is occurring over the course of therapy in normal structures (5, 6). It has thus been established that "planned dose" does not necessarily equal "delivered dose" for any given fraction or for the treatment as a whole. Moreover, changes in tumor and normal tissue during therapy suggest that the ultimate quantity of interest is D_A—particularly for normal tissues.

Remarks above notwithstanding, radiation oncology is a leader among medical disciplines with respect to the clear and quantitative specification of intervention, and the diligence pursued in the assurance that the therapy is accurately delivered (7, 8). Despite this level of consistency in dose delivery, remarkable variations in normal tissue response remain. Of course, there may also be variations in intrinsic radiosensitivity that dictate these outcomes; however, dose variation is known to affect response. This has led to the hypothesis that patient-specific estimates of D_A over the course of therapy can predict, in part, for patient-specific variations in normal tissue toxicity. Testing of this hypothesis requires the development of accurate and precise methods for dose accumulation within the human body in the presence of anatomical and morphological changes. Remarkably, a review of the literature suggests that this is not an insurmountable task, but requires a focused activity within the community if the hypothesis is to be tested for clinically important endpoints. Moreover, only careful studies that include estimates of D_A will allow us to confidently disentangle the effects of dosimetry and radiobiological sensitivity.

TOWARD ACCURATE DOSE ESTIMATION

The necessary elements to achieve routine determination of D_A include: (1) a time-dependent description of the patient anatomy and treatment parameters over the course of therapy, (2) a method to calculate the dose applied at each of those time points, and (3) the ability to generate a cumulative delivered dose distribution over the course of therapy for each small (few mm^3) subvolume of tissue. It should be noted that these elements set aside the additional complexity associated with iatrogenic cell or fluid loss over the course of therapy - a largely ignored complexity in this context.

Time-dependent descriptors of the patient anatomy and treatment

Volumetric imaging (computed tomography [CT], magnetic resonance [MR], positron emission tomography) and three-dimensional treatment planning are now elements of routine care in radiation oncology. The adoption of inverse planning techniques for intensity-modulated radiation therapy has also driven the creation of standard protocols for contouring and segmentation (9), as well as the continuing development of automated segmentation tools in the treatment planning domain (10). The development of time-dependent associations of anatomical structures is also being pursued to assist in the segmentation of time-course studies (11, 12). In addition to advances in imaging and segmentation for simulation, image-guidance technologies at the time of treatment are being

employed for directing therapy. Current systems, such as kV and megavoltage cone-beam CT, megavoltage CT, and, in the future, MR imaging, while assuring geometric targeting of the tumor, also provide a potential wealth of valuable information about the patient's normal anatomy. Thus, it is now possible to have an image-based record of the relevant anatomy at each fraction of the treatment.

However, this valuable imaging information will only contribute to dose record activities if effective, automated segmentation methods are developed to address the laborious nature of manual segmentation. The development of model-based approaches to segmentation is congruent with an important trend toward the adoption of structured descriptions or atlases of patient anatomy. Further efforts in this area do not need to be overly complex, but, rather, rigorous and unifying (13, 14). For example, the failure to develop standards for contouring of relevant anatomy (*e.g.*, inner and outer wall of rectum, or superior/inferior extent of rectum) continues to confound inter-institutional comparisons as well as intra-institutional standardization.

In addition to image-based descriptions of the patient anatomy, developments in intensity-modulated radiation therapy have required the use of electronic descriptions of the detailed treatment parameters (*e.g.*, DICOM-radiation therapy control points) that are stored within the electronic medical record and verified at each treatment fraction. In combination with the guidance images, the records provide a highly descriptive account of the treatment from which D_A could be accurately determined, provided image-guidance adjustments are recorded, the machine is operating within specified tolerances, and accurate dose calculation methods are available.

Improvements in the accuracy of dose calculation

Accurately accounting for tissue heterogeneities is fundamental to improving the modeling and prediction of dose–volume effects in radiation therapy. The accuracy of a calculated dose distribution is strongly dependent on the algorithm used to account for heterogeneities (15, 16). Monte Carlo methods, which can model the transport of radiation through all the components of the treatment unit head, as well as through the CT-based patient geometry, represent the gold standard of dose calculations (17, 18). The use of Monte Carlo dose calculations for research studies prospectively and even retrospectively is growing (19, 20). The benefits of which are expected to be realized in regions of substantial tissue heterogeneity (*e.g.*, for lung or head-and-neck treatments), as well as in low dose (21) or out-of-field regions (22). Despite calculation advances, currently used dose–volume constraints are typically based on data largely calculated either without any accounting for tissue heterogeneities, or using very simple methods (23-25). The impact of heterogeneity corrections, or the type of heterogeneity corrections, on the dose–volume analysis of treatment outcomes is poorly studied. Recent work shows that tumor control probability modeling was affected by the underlying dose calculation accuracy (retrospective Monte Carlo–based corrections vs. path-length based corrections) (26). As its use propagates, proton therapy will not only alter the dose to normal tissues and contribute to our understanding of dose–volume effects, but also highlight the dose computation challenges that remain for this technology (27).

Development of tissue deformation and tracking tools

The development and validation of deformable registration algorithms has enabled tracking of mobile tissues over the treatment course and, in some cases, during the treatment fraction. Tissue deformation tracking can improve the accuracy of D_A for both the target volume and the critical normal tissues. Validation of these methods is typically achieved using intrinsic features (*e.g*., bifurcations in blood vessels) or fiducials (*e.g*., gold markers) that can be confidently localized and compared with the deformation estimate of displacement (28, 29). The lung presents a unique challenge as the volume changes substantially between inhale and exhale. Studies have investigated the effect of different interpolation methods on the accumulation of dose with changes in volumes (30). Using four-dimensional cone beam CT images (31) or, in the future, dynamic MR imaging (32), obtained at each treatment fraction should improve the accuracy of the D_A distribution by modeling the breathing motion and the residual setup uncertainties that cannot be accounted for with simple couch corrections. Geometric tracking of tissue over the course of treatment becomes increasingly difficult in the presence of large changes in tissue volume (33, 34). Ultimately, the deformation algorithms need to address challenges such as, hollow organs (bladder, rectal wall, small bowel), changes in volume (*e.g*., liver), varying organ substructure (*e.g*., lobes of liver and lung), and, mechanical perturbations brought about by the disease (cancer or comorbidity).

OPPORTUNITIES AND NEEDS

Robust and streamlined methods for accurate accumulation of dose

As described previously, the literature demonstrates the feasibility of generating a record of D_A. However, significant labor is currently required to perform these studies. Contouring and segmentation methods need to be developed that allow these activities to be pursued at reasonable workloads, preferably in a proactive fashion during the course of therapy, even on a fraction-by-fraction basis. This level of performance would integrate dose accumulation into the patient management workflow and also enable online planning activities. Visual and quantitative summaries of the segmentation results should be made available. These should require a minimum of effort to evaluate through efficient access (*e.g*., web-based) and work list management.

Advancing the performance of deformation modeling requires both additional information and the creation of quantitative tools. The development of novel image-based methods of measuring deformation and the underlying mechanical characteristics of normal and diseased tissues should be pursued. The trend toward high dose per fraction stereo-tactic body radiation therapy will heighten risks associated with occasional anatomical displacements. The development of multiorgan system deformation models and dose tracking will become of greater importance in these areas as the field pushes for broader application of stereotactic body radiation therapy methods. The validation of these more complex systems will require both the development of phantoms that reflect realistic anatomical changes and the collection/sharing of large deformation datasets that contain “ground truth” estimates of the deformation. In the development and publication of these methods, investigators should clearly specify the documented performance of their

algorithms and the conditions under which the algorithms are not likely to perform well (*e.g.*, volume change, slipping surfaces).

Development of novel dosimetry systems for validation of dose calculations

The validation of these dose tracking methods and the assurance of their performance over a range of spatial scales should also be a priority for the field. Recent advances in dosimeter technologies, such as implanted metal-oxide-semiconductor field-effect transistor MOSFET detectors (35), optical point (36), and volumetric methods (37), MR-based gel technologies (38), and carbon-nanotube approaches (39, 40) offer the promise of validating accumulated delivered dose distribution in phantoms or patients. Incorporating deformation and dose validation phantoms (41) is likely to be necessary to evaluate the end-to-end performance of these systems.

Novel metrics for characterizing dose estimation accuracy and precision

Dose accumulation methods will always be imperfect due to challenges of calculation in complex geometries (*e.g.*, heterogeneities in atomic number), absence of imaging data to describe the geometry of the patient (*e.g.*, missing volumes or motion that exceeds the sampling rate), or weaknesses in the machine model being employed. D_A estimates need to be accompanied by companion uncertainty estimates. The development of methods to describe confidence intervals on the dose and volume data could be used to extract higher quality sub-datasets from patient studies and ask more specific questions. Furthermore, sensitivity analyses could be applied to estimate the dose uncertainty corresponding to these various conditions and would be a valuable input to outcomes modeling activities. It should be noted that even simple parameters, such as weight loss, patient treatment protocol (*e.g.*, use of bowel preparation in prostate cases to understand the degree of variation rectal dose delivered), or the use of heterogeneity corrections in the dose calculation would all represent important qualifiers of the four-dimensional dose record.

Uncertainty analysis should not be restricted to the dose accumulation activity. The development of predictive schemes that estimate the uncertainties in the *planned* dose distribution would also be of value to the field. These calculations would require, however, the establishment of a model and database of geometric uncertainties (systematic and random components; potential trends; both target and normal structures) for the patient population and treatment facility to which the individual patient corresponds. It is reasonable that such a tool would be integrated within the planning systems architecture and the resulting uncertainties recorded in the electronic treatment planning records for subsequent consideration in outcomes analysis.

Dose and volume as a predictive factor in multivariate analyses

It is known that other factors, besides dose, are crucial to an understanding of outcome variability. Advances in our understanding of molecular biology and the development of genomic and proteomic analyses of patient tissue carry significant promise (42). However, depending on the relative scale of these effects, it may not be possible to isolate such a dependence in the presence of large undocumented variations in another important variable, such as D_A (43). The linkage between simple variables such as dose and volume have been

demonstrated to correlate with proteomic assays collected during radiation therapy (44). Maximizing sensitivity for biomarker validations will require accurately controlling for the differences between “certain dose distributions” and “uncertain dose distributions,” as measured along a continuum. The ability to routinely follow patient cohorts with precise and accurate dose tracking is thus a prerequisite for fully benefiting from genomic and proteomic studies of normal tissue radiosensitivity. Hence, these records need to be of sufficient flexibility to allow complex volume (alternative structures [*e.g*., portions of the lung]) and time dependent effects (*e.g*., variations in dose rate across intensity-modulated radiation therapy practice) to be integrated into the analysis.

SUMMARY

The goal of generating accurate D_A distributions to target and normal tissues as a part of routine radiotherapy practice is feasible. However, key research and development areas need to be accelerated, including: auto-segmentation, deformation modeling, dose accumulation, dose calculation in complex environments, and methods of estimating the uncertainty in the accumulated dose distribution over the course of therapy. In addition to these research initiatives, informatics developments are necessary to make the tracking of dose a feasible and viable activity, including, support for workflow tools that allow automated image segmentation and dose accumulation with efficient review and validation. Finally, the efforts will not succeed without a corresponding level of investment in the leadership required to formulate standardized methods and nomenclature to allow the volumetric results to be compared in a direct and productive fashion. It should go without saying that accomplishing the goal of accurate normal tissue dose response would also assist in tumor dose-response characterization, provide methods for adaptive approaches, and eliminate a confounding variable in studies of individualized normal tissue radiosensitivity. Accurately estimating D_A is a critical element in the drive to maximize the performance and safe application of radiation therapy for the individual patient.

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