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Editorial

Towards spatial representations of dose distributions to predict risk of normal tissue morbidity after radiotherapy

Design of clinical trials and definition of new standards of care in radiotherapy have historically been driven by the balance between doses delivered to the target volume against doses delivered to the healthy organs surrounding the tumour. State-of-the-art high-precision radiotherapy, together with other advances in cancer therapy, have led to improved clinical outcomes [1].

In the setting of conventionally fractionated radiotherapy, dose distributions within target volumes are reasonably uniform [2]. In contrast, normal tissue dose distributions are highly non-uniform and their shape can be tailored while still achieving planning goals. These planning goals are typically formulated in terms of dose-volume constraints which drive optimization towards treatment plans deemed best for each patient. Visual inspection of how isodose lines are shaped around target volumes and into normal tissues is an integral part of plan checking and approval. Most radiotherapy plan optimization, evaluation and outcome analysis have been based on summarizing 3D dose distributions into dose-volume histograms (DVH). This approach has been successfully used to describe and utilize dose-volume-response relationships [3].

Limitations of DVH-based outcome assessments are well known. The DVH strips away geometry information, i.e. every region of normal tissue is seen as equally important, and no cross-talk between regions is considered. Clinical data support existence of regional effects, although explanations for these effects remain elusive [4,5]. Commonly used rationale to justify more sophisticated approaches relies on one or more of the following, and to a certain extent overlapping, arguments: 1) functional burden is not uniformly distributed in normal tissues; 2) stem cells capable of rescuing normal tissue function are primarily concentrated in particular parts of normal tissue; 3) organs which are contoured as a whole are in fact anatomically/geometrically substructured, e.g., lobes in lung or tracts in brain, and risk of morbidity does depend on which substructures receive dose; 4) parts of an organ are differentially sensitive to radiation; 5) morbidity is related to radiation-induced damage to organs other than ones for which DVHs are evaluated; 6) spatial distribution matters, e.g. small hot spots spread out on the rectal surface might have different consequences compared to larger, spatially clustered patterns.

Dose-volume-response relationships that also incorporate the geometrical information of dose distributions have therefore received considerable interest. The first studies including geometrical information in normal tissue complication probability (NTCP) models utilized dose surface maps (DSMs), and were focused on hollow organs, in particular to study bladder and rectum dose-volume-response relationships following radiotherapy for prostate cancer [6–8]. Therefore, utilization of DSMs has helped to demonstrate that the dose delivered to the caudal part together with shape and extension of the hot spots over rectal wall are related to an exacerbation of morbidity [9–13]. Similarly, doses delivered to the trigone area and the urethra were found to play a major role in the overall worsening of genito-urinary symptoms following radiotherapy for prostate cancer [14–18]. Overall, DSMs are often used in an empirical approach, exploiting significant differences in dose distribution patterns between patients with and without morbidity to identify regions which might correspond to substructures governing the dose response. In the search for methods to include geometrical information into NTCP models, a more theoretical or deterministic approach can also be considered. A deterministic approach hypothesizes that an organ/tissue is composed by subunits with different radiosensitivity, with one (or more) playing a major role in the manifestation of morbidity. Therefore, damage to an identified substructure(s) may trigger manifestation of the observed morbidity.

This issue of the journal presents the first study describing the impact of dose to heart substructures on the overall survival rate [19]. Cardiac disease associated with radiation has been observed in cancer patients treated to thoracic and abdominal regions, i.e. breast cancer and lymphoma patients, because they are typically long-term survivors, providing most of the outcome data. The QUANTEC report on the heart provided dose-volume guidelines for two endpoints: pericarditis and long-term cardiac mortality [5]. For the former, mean dose < 26 Gy and $V_{30Gy} < 46\%$ were suggested. Cardiac mortality, in contrast to pericarditis, appears to exhibit a weak volume effect. This observation has led to substantial changes in how radiotherapy is delivered to left-sided breast cancer patients. Heart blocks including the “no heart in beams-eye-view” policies have been adopted, deep inspiration breath hold and treating prone techniques have also been used to spare the heart. The QUANTEC heart paper proposed a $V_{25Gy} < 10\%$ constraint to control the “tail” of the DVH [5], however, this constraint has been later shown to not fully protect against the probability of cardiac mortality $< 1\%$ in breast cancer patients [20]. This also underlines another deficiency in using DVH constraints. Various endpoints exhibit different dose-volume response. Consequently optimizing, e.g. mean dose, will reduce probability of pericarditis but is not sufficient to control the risk of cardiac mortality. Identifying an endpoint of the greatest concern or with the tightest constraints is one possible way but it may become too restrictive.

For the heart also the initial definition and delineation of the organ at risk is challenging. Specifically, the whole heart can be contoured, while also the pericardium (often defined as a “shell” expansion of the heart contour), the left ventricle, coronary vessels or specifically the left anterior descending coronary artery are used in different protocols and institutions [5]. Different endpoints have been connected to anatomical

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features and functionality, for example the pericardium is likely appropriate for pericardial effusion and the left anterior descending artery for ischemic heart disease [20]. However, dose-volume parameters for different structures behave in a correlated manner which complicates search for the "guilty" party, and a full mechanistic understanding of how morbidity develops is lacking.

Searching for regional effects may provide us with a guide to selective sparing of either structures, or geometrically defined sections of the organ. Because multiple anatomically/geometrically defined structures/regions must be analysed for different endpoints, automation might be required. Auto-contouring not only allows us to tackle a laborious task of delineating structures which are not routinely delineated in clinical practice, it may also improve consistency [21]. Additionally, auto-contouring tools included in retrospective analysis will pave the way to interrogating outcomes data and will further promote prospective use for selective regional sparing [22].

An overall aim of dose-surface based outcome studies is to identify the substructures of the organ that play a key role in dose–response relationships, and from there provide robust metrics to be used in plan optimisation. Most studies in this field have applied a voxel-wise analysis to quantify significant dose differences [10–15]. Voxel-based data mining of radiotherapy doses relies on the comparison of delivered dose distributions, aggregated over subgroups of patients with and without the morbidity endpoint of interest. Such aggregation requires a common frame of reference, which is chosen based on the anatomy of the organ and the nature of the endpoint of interest. For hollow organs simplified spherical or cylindrical geometries are common, allowing for an easy anatomical interpretation of results. In case such simplified geometries are unable to capture the relevant effects, more sophisticated methods based on validated deformable registration techniques may offer increased statistical power [15]. As these typically have much larger degrees of freedom, careful validations should be performed to prevent overfitting. A next challenge is the estimation of the actually delivered dose to tissues in the chosen frame of reference; often only treatment planning geometries and dose distributions are available, which in the case of a highly mobile organ may only offer a rough estimate. Leveraging treatment room imaging modalities (e.g. cone-beam computed tomography or magnetic resonance imaging guided systems) may improve these estimates and hence strengthen the statistical associations between doses and the morbidity endpoints [9,12,23,24].

Estimation of the significance of an observed difference in population average doses over the outcome subgroups (controlling the multiple testing issues introduced by the large numbers of voxels analysed) is generally established using a permutation-based approach, randomly re-shuffling patients between the morbidity and non-morbidity subgroups [25]. The associated p-value indicates per voxel significant dose differences. One generally (ad-hoc) selects a seemingly relevant threshold of the test statistic (e.g. local dose difference divided by standard deviation) and selects voxels in the observation which exceed this value. It should be noted that all subsequent (statistical) modelling using these selected voxels should be interpreted with care; even for a subset of voxels which have a large dose difference merely by chance, subsequent modelling would lead to erroneous, but seemingly significant dose–effect relations and survival analyses.

Attempts can be made to interpret the observed dose difference patterns in terms of an underlying anatomical or biological cause; a crucial, and likely the most difficult step of the dose data mining methodology. Suppose one would analyse a group of prostate cancer patients who had all been "ideally" irradiated, so with an optimal compromise between tumour control probability and risk of morbidity, and one would construct rectum morbidity dose difference maps. Patients with less favourable anatomy would have received high dose to a larger fraction of the rectum wall, leading to higher morbidity rates, and dose distributions might appear slightly shifted compared to those from patients with more favourable anatomy. These dose difference regions illustrate the well-known fact that dose causes morbidity, and merely pin-point the locations where dose variations exist due to patient specific anatomies and limitations of the applied external beam radiotherapy modality [11,14,15]. Misinterpretation of these locations as dose avoidance regions, e.g. loading these patterns into a treatment planning system to steer dose elsewhere, could deteriorate the (already optimal) treatment plans and lead to less favourable clinical outcomes. Rather, observed patterns should serve as the basis for an informed hypothesis of the mechanisms underlying the clinical manifestation of morbidity; e.g. in the way these patterns align with potentially critical substructures of the organ. Next, prospective tests should be devised to validate these findings before being incorporated into NTCP models which may then improve radiotherapy for future patients.

Further attention should be paid to the possible impact of differences between planned and delivered doses, mainly driven by organ motion. In many cases statistically significant local dose effects are found in sub-regions where the positioning of organs is more stable [14,26]. This enhances the chance of finding statistically significant differences in the doses between patients with and without morbidity because in those more stable sub-regions the planned dose is similar to the delivered dose. An explicative situation is given by the non-isotropic motion of the bladder due to its variable filling, with the base being relatively stable while the cranial portion showing large variations. This fact entails lower systematic errors (planned vs. delivered dose) in the high dose region which corresponds to the bladder base [26]. Results on local dose effects for the bladder base/trigone could thus also be due to the higher reliability of the investigated features (doses at the pixel level) in the motion-stable region, with doses to the bladder dome coming out as not significant due to the limited correspondence between planned and delivered doses. Systematic studies on organ motion and on differences between planned and delivered dose could help in discriminating between biologically relevant local dose effects and effects driven by the inaccurate description of delivered doses in some regions [27,28].

DSMs might increase predictive power of normal tissue dose response relationships. New findings from voxel-based data mining should be accompanied by studies on organ motion, on estimation of differences between planned and delivered dose and on the possible biological role of the regions identified as significantly associated with an increased risk of radiation-induced morbidity. Finally, generalisability studied on a suitable number of independent cohorts will pave the way to clinical applications of the results.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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