Radiotherapy and Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Three-dimensional cluster formation and structure in heterogeneous dose distribution of intensity modulated radiation therapy ☆

Ming Chao [a,*], Jie Wei [b], Ganesh Narayanasamy [c], Yading Yuan [a], Yeh-Chi Lo [a], José A. Peñagarícano [c]

[a] Department of Radiation Oncology, Mount Sinai Medical Center, New York; [b] Department of Computer Science, City College of New York; and [c] Department of Radiation Oncology, University of Arkansas for Medical Sciences, Little Rock, USA

ARTICLE INFO

Article history:
Received 31 August 2017
Received in revised form 12 March 2018
Accepted 13 March 2018
Available online xxxx

Keywords:
Intensity modulated radiation therapy
Heterogeneous dose distribution
Dose–volume histogram
Normal tissue complication probability
Cluster model

ABSTRACT

Purpose: To investigate three-dimensional cluster structure and its correlation to clinical endpoint in heterogeneous dose distributions from intensity modulated radiation therapy.
Methods: Twenty-five clinical plans from twenty-one head and neck (HN) patients were used for a phenomenological study of the cluster structure formed from the dose distributions of organs at risks (OARs) close to the planning target volumes (PTVs). Initially, OAR clusters were searched to examine the pattern consistence among ten HN patients and five clinically similar plans from another HN patient. Second, clusters of the esophagus from another ten HN patients were scrutinized to correlate their sizes to radiobiological parameters. Finally, an extensive Monte Carlo (MC) procedure was implemented to gain deeper insights into the behavioral properties of the cluster formation.
Results: Clinical studies showed that OAR clusters had drastic differences despite similar PTV coverage among different patients, and the radiobiological parameters failed to positively correlate with the cluster sizes. MC study demonstrated the inverse relationship between the cluster size and the cluster connectivity, and the nonlinear changes in cluster size with dose thresholds. In addition, the clusters were insensitive to the shape of OARs.
Conclusion: The results demonstrated that the cluster size could serve as an insightful index of normal tissue damage. The clinical outcome of the same dose–volume might be potentially different.
 Radiotherapy and Oncology xxx (2018) xxx–xxx

In radiotherapy, the dose–volume histogram (DVH) is used routinely to evaluate the quality of a treatment plan [1]. In the past years, new treatment techniques have been under continuous developments, showing improved treatment outcomes. The reliance on DVH, however, has not been challenged. In radiation therapy, unlike target volumes that usually receive a uniform dose distribution, normal tissues surrounding the designated treatment volume may receive appreciable, and spatially, inhomogeneous doses. Normal tissue complication probability (NTCP) models have been developed to evaluate the potential risk of normal tissue injury [2–8]. Similar to DVHs where no information on the spatial location of the absorbed dose is revealed, current NTCP models do not account for the location and size of killed functional sub-units (FSUs) [9]. It is, therefore, possible to have the same DVH or NTCP for two distinct inhomogeneous dose distributions that could yield different clinical outcomes. Furthermore, from NTCP presentation alone, there is no way of knowing the percentage of tissues receiving the high doses and the locations of the "hot spots" (region receiving over 100% of prescription dose). Another important quantity that is commonly employed in evaluating inhomogeneous dose distributions is the equivalent uniform dose (EUD), which was initially introduced for the tumor, but later was generalized to the organs at risk (OARs) [5,10,11]. While sensitive to the irradiation dose and volume, EUD falls short in providing sufficient information to assess whether the treatment is tolerable [11].

Cervical spinal cord irradiation in rat models has demonstrated that for a large inhomogeneous dose distribution, the dose that produces half maximal response D_{50} for injury is reduced [12–14]. This appears to be the consequence of a small volume irradiated to a large dose, adjacent to a large volume irradiated to a smaller dose. Although unproven in humans yet, these findings emphasize the importance of the spatial distribution of the absorbed dose that is not reflected by either of the aforementioned plan evaluation metrics. The location and size of killed FSUs within the OARs could be important for patient safety as well as clinical outcome [15,16]. Therefore, categorizing tissues into serial or parallel architectures may be inadequate [12,17].

☆ The work was presented at the 59th Annual American Association of Physicists in Medicine (AAPM) Meeting in Denver, CO, July 30–August 3rd, 2017.

* Corresponding author at: Department of Radiation Oncology, Mount Sinai Medical Center, New York, NY 10029, USA.
E-mail address: ming.chao@mountsinai.org (M. Chao).

https://doi.org/10.1016/j.radonc.2018.03.011
0167-8140/

For computed tomography (CT)-based treatment planning, radiation dose is calculated in a pre-selected three-dimensional (3D) grid consisting of a number of small rectangular volumes called voxels [18,19]. For voxels of OARs near the tumor, the doses can be high as well. The aggregates of these high dose voxels, denoted by *clusters*, might correlate with normal tissue complications. Since cluster formation is the foundation of cluster models, it is imperative, thus the aim of this paper, to investigate how the clusters are formed in a clinically relevant scenario of OAR receiving inhomogeneous dose. The secondary goal is to establish cluster size as a metric of normal tissue dosage.

Methods and materials

Examination of OAR clustering patterns near the tumor

To explore the dose–volume effect from clinical dose distributions, we calculate cluster sizes of three OARs close to the planning target volumes (PTVs) that share similar DVH distributions. Plans from ten head and neck (HN) patients are employed for this study as shown in group I of Table 1 where four groups of patients are employed in this study. Eclipse TPS (Varian Medical Systems, Palo Alto, CA) is used in intensity modulated radiation therapy (IMRT) planning for a prescription dose of 66 Gy covering 98% PTV. HN cancer makes up a significant fraction of cancer cases treated with radiation, and the study of esophageal spatial dose distribution, for instance, may assist in better understanding of the long-term potential radiation damage [20]. The OARs investigated are esophagus, right and left parotids. The plan data are exported from the planning system to a MATLAB based software *CERR* for processing [21]. For each OAR or PTV, a 3D cluster searching algorithm is performed and its cluster size is computed based on the three-connectivity choice. While adopting the same definition of cluster and connectivity as described in [17], we further extend it to the 3D situation (Refer to Appendix A for details). Four dose thresholds, 40 Gy, 50 Gy, 60 Gy and 66 Gy are adopted to evaluate the clustering patterns. Additionally, five plans are generated using the multicriteria optimization (MCO) in RayStation TPS (RaySearch Labs, Sweden) based on a single HN case (group II of Table 1). Similar evaluation strategy is employed to examine the clustering patterns.

Correlation of OAR cluster size to radiobiological parameters

We focus on the upper-five-centimeter of the esophagus (overlapping with or close to PTV) in another ten HN patients treated at Mount Sinai Hospital (MSH) as shown in group III of Table 1. IMRT technique is used for these patients for prescription: 70 Gy in 35 fractions to the PTV. The dose constraint on the esophagus is limited to a mean dose of 36 Gy. We choose the upper-five-centimeter of the esophagus to calculate the biological indices, including NTCP with LKB model [2,3] (for the NTCP calculation: parameter n = 0.67, D50 = 21 Gy and m = 0.59) and EUD [11] to compare with the maximum and mean doses, respectively. We compute the sizes of the largest clusters with one-, two-, and three-connectivity using 60 Gy threshold dose, and analyze their relationship with the radiobiological parameters.

Monte Carlo simulation study

In clinical treatment planning, the dose distribution of the OAR is fixed once the final calculation is performed. Accordingly, there is a specific DVH and a fixed cluster structure. To investigate the clustering pattern for a given DVH, a large number (10 K) of dose distributions from MC simulations are needed. The differential DVHs of the studied OARs are exported. Next, each of these OARs is converted to a binary image whose voxel values inside the OARs are set to 1 and 0 otherwise. The binary image is used to determine whether each voxel in the 3D dose grid belongs to the OAR or not. The histogram is used as a probability mass function for event generation. A dose threshold, the fractional density defined as the ratio of voxels receiving a dose larger than a chosen dose threshold, is used in the MC studies. A cluster searching algorithm (detailed in Appendix B) is implemented to explore the cluster formation and structure.

Results

The results of cluster patterns for PTV, and the OARs, including right and left parotids, and esophagus, are shown in Fig. 1 for the first ten HN patients. The vertical axis is the normalized three-connectivity cluster size in 3D, whereas the horizontal axis represents four dose thresholds: 40 Gy, 50 Gy, 60 Gy and 66 Gy. The distributions of cluster sizes from PTV for ten patients appear almost identical, while large differences are observed for the OARs. The right parotid and esophagus for the second patient and the left parotid for the fifth patient are geographically closer to their PTVs than other patients, so their cluster sizes are slight larger at higher dose thresholds compared with other patients. Nevertheless, no overall consistent clustering is observed in OARs among these patients, regardless of the similar PTV clustering patterns.

Five treatment plans created in MCO having identical PTV dose distribution but slightly different doses to the OARs is investigated for group II in Table 1 (patient 11). Displayed in Fig. 2 is the normalized cluster size as a function of similar dose thresholds in three-connectivity scenario. Results based on the MCO plans are depicted in Fig. 2 where similar clustering patterns exist for all three OARs, indicating the relative positional variations in dose distribution play a significant role in the cluster patterns.

Next, we examine the correlation of cluster sizes with the radiobiological parameters using the upper-five-centimeter esophagus for patients 12–21 in group III in Table 1. Depending on the relative position of the esophagus and the PTV, the DVH of esophagus could vary. For patient# 12, the inferior part of esophagus overlapped with the PTV, such that a significant portion received a high dose,

Table 1
List of four groups of patients used in the clinical study (groups I–III) and Monte Carlo simulation (group IV).

Group	Patient List	Type	Structure of Interest	Prescription	Purpose	Data Source
I	1–10	Head and Neck	Esophagus, Parotids, PTV	2.2 Gy × 30 fractions	Clustering pattern	U. of Arkansas for Medical Sciences
II	11	Head and Neck	Esophagus, Parotids, PTV	2.2 Gy × 30 fractions	Clustering pattern	U. of Arkansas for Medical Sciences
III	12–21	Head and Neck	Upper-5 cm Esophagus	2 Gy × 35 fraction	Correlation with radiobiological parameters	Mount Sinai Hospital
IV	22	Hemithorax	Esophagus, Heart, PTV	1.8 Gy × 22 fractions	Monte Carlo Simulation	Mount Sinai Hospital

Please cite this article in press as: Chao M et al. Three-dimensional cluster formation and structure in heterogeneous dose distribution of intensity modulated radiation therapy. Radiother Oncol (2018), https://doi.org/10.1016/j.radonc.2018.03.011