Original Article

Voxel based BED and EQD_2 Evaluation of the Radiotherapy Treatment Plan

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Abstract

Introduction: Three-dimensional (3D) treatment planning of patient undergoing radiotherapy uses complex and meticulous computational algorithms. These algorithms use 3D voxel data of the patient to calculate the radiation dose distribution and display it over the CT image dataset for treatment plan evaluation. **Aims and Objective:** The purpose of the present study is the development and implementation of radiobiological evaluation of the radiotherapy treatment plan incorporating the tissue-specific radiobiological parameters. **Material and Method:** An indigenous program was written in MATLAB® software (version 2011b of Mathworks Inc.) to extract the patient treatment plan data from DICOM-RT files which are exported from the treatment planning system. CT-, Structures- and Dose-Cube matrices are reconstructed from the exported patient plan data. BED and EQD_2 based dose volume histograms (DVHs), colorwash and iso-effective dose curves were generated from the physical Dose-Cube using the linear-quadratic (LQ) formalism and tissue-specific radiobiological parameters (α/β). **Results and Conclusion:** BED-and EQD_2-colorwash and iso-effective curves along with BED and EQD_2 dose volume histograms provide superior radiobiological information as compared to those of physical doses. This study provides supplementary recipes of radiobiological doses along with the physical doses which are useful for the evaluation of complex radiotherapy treatment plan of the patients.

Keywords: BED-colorwash, BED-volume histogram, DVH, EQD_2-colorwash, EQD_2-volume histogram, iso-BED curve, iso-EQD_2 curve

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Introduction

Radiotherapy (RT) treatment plan evaluation generally depends on the clinical experience of radiation oncologists and medical physicists. Conventionally, plan evaluation was done based on the analysis of physical dose distribution. However with the development of radiobiological models, the trend is shifting from the physical dose to radiobiological dose evaluation of the RT treatment plan. Digital imaging and communication in medicine in RT (DICOM-RT) is an extension of DICOM standard files which provides compressed information of RT Plans (RPs) consisting of various files such as Computed Tomography (CT) images, RT Structure Set (RTSS), RP, and RT Dose (RD).[1] Most of the treatment planning systems (TPSs) use DICOM-RT format to save the treatment plan data.[2] As the paradigm shifts from the two dimensional (2D) to three-dimensional (3D) and four-dimensional (4D) TPS, the role of 3D- and 4D-volumetric data in the TPS needs new methods of visualization of 3D-and 4D-image datasets.[3] 3D visualization needs voxel-based display of 3D image dataset which is reconstructed using CT images in DICOM format. Most widely used methods for treatment plan evaluation are slice by slice visualization of dose colorwash, dose volume histograms (DVHs) and plan quality metrics.[4,5] With the availability of clinical data and advancement in the computation techniques, the method of plan evaluation has been shifted from the physical dose evaluation to radiobiological dose evaluation. 2D TPS data was not sufficient to provide the information of the irradiated volumes and doses. With the help of 3D TPS, it is possible to generate the dose and volume information of different irradiated organs and target volumes. Contouring of the different organs and target volumes in 3D TPS provides the quantitative assessment

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of the dose distributions inside these volumes. Voxels inside the contours of different organs and target volumes give the information about the dose distribution on different voxels which is used to develop the DVHs. There are only a few commercially available software packages which provide biological optimization tools, radiobiological equivalent dose of 2 Gy (EQD_2) and biological equivalent dose (BED) volume histograms. There is currently no commercial software which displays both BED-and EQD_2-colorwash as well as iso-BED and iso-EQD_2 curves over the CT image dataset along with physical dose distribution.

In this study, BED-and EQD_2-colorwash and iso-BED and iso-EQD_2 dose curves were generated from the voxels of each contoured structure extracted from DICOM-RT radiotherapy treatment plan and displayed over the CT image dataset in addition with BED-and EQD_2-volume histograms for the evaluation of different treatment plans.

Materials and Methods

Voxel-based Radiobiology display (VRb) tool for radiotherapy treatment plans evaluation is an independent platform which can display physical dose-, BED-and EQD_2-colorwash and iso-physical dose, iso-BED, and iso-EQD_2 curves on the 3D image dataset. BED-and EQD_2-colorwash used physical doses of voxels associated with the different contoured target and organ volumes and tissue-specific parameter (α/β). Physical dose distribution matrix (or Dose-Cube) obtained from the RT Dose file was converted into BED-and EQD_2-Cube.[6] A program has been written in MATLAB® software version R20011b (The MathWorks, Natick, MA), and some of the code snippets have been taken from the Computational Environment for Radiotherapy Research (CERR) and matRad (open source TPS) programs written in MATLAB software.[7,8]

Preprocessing of the DICOM-RT files

In this work, a patient of carcinoma cervix was chosen retrospectively to demonstrate the proposed method. The patient was treated with volumetric modulated arc therapy technique using 6 MV photon beam of Varian medical linear accelerator (Trilogy), Palo Alto, CA, USA. Eclipse TPS version 11.0 (Varian Medical System, Palo Alto, CA, USA) was used for the treatment planning of the patient. The total physical dose of 46 Gy in 23 fractions was delivered to the patient with five fractions/week treatment protocol. Progressive resolution optimizer version 3 (Varian Medical System, Palo Alto, CA, USA) and Analytical Anisotropic Algorithm were used for optimization and dose calculation of the treatment plan with 2.5 mm dose grid size resolution, respectively. The patient plan was exported in the DICOM-RT format including CT images, contoured structures, and absolute Dose-Cube using patient plan export filter in Eclipse TPS. DICOM-RT files were processed using the MATLAB® software. The following steps were used to process the DICOM-RT files.

1. Exported DICOM-RT files of the patient plan consists of a set of CT files containing axial CT images, Dose file (RD.dcm) having information of physical dose distribution matrix and physical DVHs of all the contoured structures of the treatment plan, RT-Plan file (RP.dcm) containing the information of plan parameters, number of fractions, number of beams, dose prescription, and RTSS file having the information of the different contoured structures of the organs at risk (OARs) and target volumes were imported in MATLAB software.
2. Extracted information from CT-, RD-, RP-, and RTSS-files was stored in a structured array based on their parameters in DICOM-RT files. The array contained all the information regarding patient, machine and treatment plan parameters of DICOM-RT tags such as modality, patient identifiers (ID), series instance unique ID (UID), service-object pair (SOP) instance UID, series number, pixel spacing (PS), slice thickness, dose type, reference dose sequence and reference SOP instance UID, etc.
3. Data for CT-, Structures-and Dose-Cube matrices were generated from DICOM-RT files using different tags of the DICOM file format like Image Position Patient (IPP), PS, slice thickness, Structure Set region of interest (ROI) sequence, ROI contour sequence, dose grid scaling, rescale intercept and slope, etc.

Reconstruction of CT-, Structures-and Dose-Cube

Imported p number of CT images having dimensions of m × n pixels matrix, with the constant value of slice thickness were stacked together in the increasing order of slice positions to create the CT-Cube matrix (3D matrix) of dimensions m × n × p. For example, for a given CT scan series of 122 axial CT images, each image having 512 × 512 pixels matrix was stacked to form a CT-Cube matrix (3D matrix) of 512 × 512 × 122 dimensions. Structures-Cube was reconstructed using the contour data points of all the delineated structures (OARs, planning target volume [PTV] and others) obtained from the RTSS file. For each contoured structure, digitized coordinates were extracted slice by slice and linearly interpolated with respect to the resolution of the CT-Cube. Dimensions of the Structures-Cube were kept as same as that of the CT-Cube. Physical Dose-Cube was obtained directly from the RD file and reconstructed to the same dimensions and resolution as that of the CT-Cube using 3D interpolation. Number of fractions and prescribed dose of the plan were also extracted from the RP file of the patient treatment plan.

Conversion of physical Dose-Cube into BED- and EQD_2-Cube

Physical Dose-Cube of dimensions m × n × p was obtained after the preprocessing of the DICOM-RT files. For the conversion of physical Dose-Cube into EQD_2-and BED-Cube, predefined values of α/β were assigned as 3 Gy and 10 Gy for each contoured organs and target volumes, respectively.[9] The user can also modify the default values of α/β in the in-house program. The physical dose of each voxel inside the contoured structures was converted into

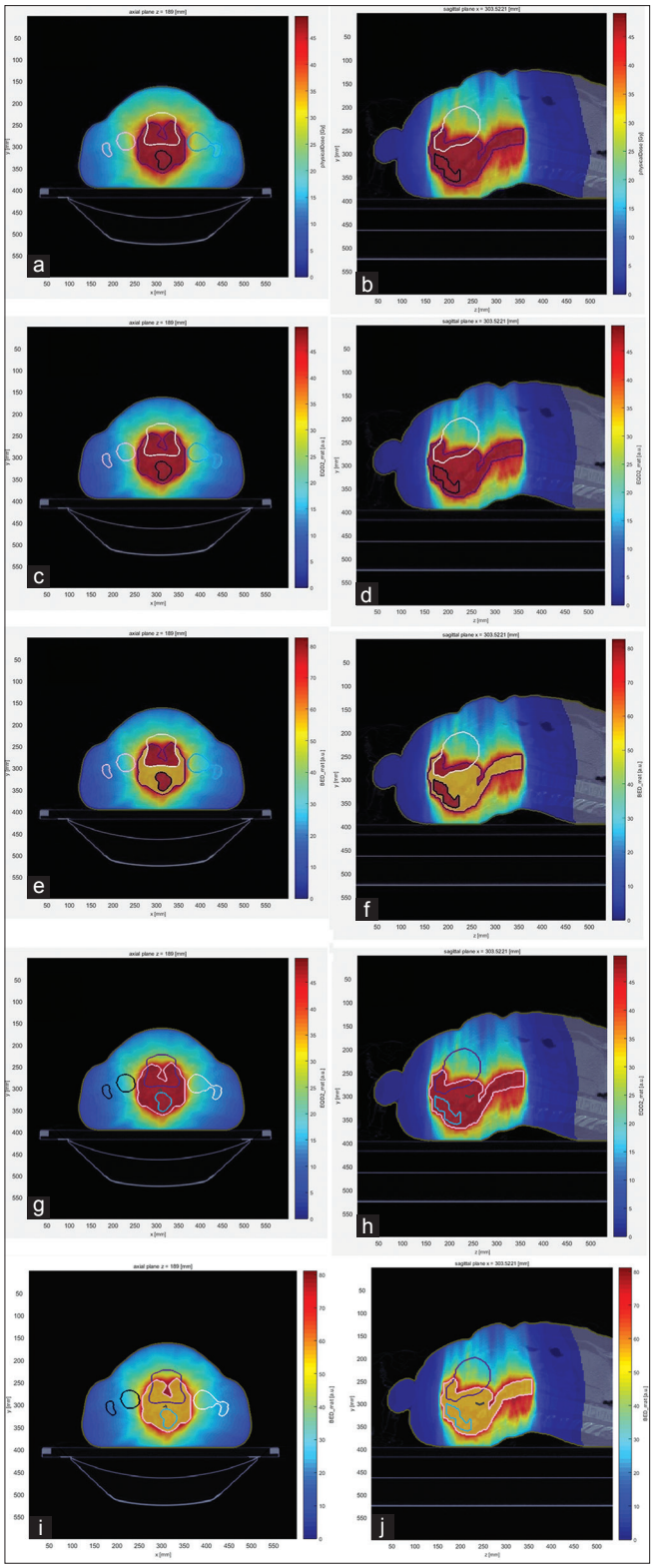

Figure 1: Physical dose colorwash (a and b), EQD_2-(c and d), BED-(e and f) colorwash with special priority given to OARs radiobiology and EQD_2-(g and h), BED-(i and j) colorwash with special priority given to PTV radiobiology over an axial and sagittal slice of treatment plan of a carcinoma cervix patient, respectively

the EQD_2 and BED by incorporating α/β values of the different contoured volumes and number of fractions (n).

The conversion of physical dose of an arbitrary i^{th} voxel into $BED_{voxel}\ (i)$ of the same voxel is given by the mathematical relationship[5,6]

$$BED_{voxel}(i) = n \times d_{voxel}(i) \times \left(1 + \frac{d_{voxel}(i)}{\alpha/\beta}\right) \quad (1)$$

where $BED_{voxel}\ (i)$, $d_{voxel}\ (i)$ represent the BED, physical dose per fraction of the i^{th} voxel in the patient treatment plan respectively, and α/β is the corresponding tissue-specific radiosensitivity parameter of linear quadratic model. i is the index of any arbitrary i^{th} position of a voxel taken from the product of the m × n × p voxels. Similarly, the physical dose of i^{th} voxel is converted into the $EQD_{2,\,voxel}\ (i)$ by the following mathematical expression

$$EQD_{2,voxel}(i) = n \times d_{voxel}(i) \times \left[1 + \frac{d_{voxel}(i)}{\alpha/\beta}\right] \Big/ \left[1 + \frac{2}{\alpha/\beta}\right]$$
$$= BED_{voxel}(i) \Big/ \left[1 + \frac{2}{\alpha/\beta}\right] \quad (2)$$

where $EQD_{2,\,voxel}\ (i)$ is the radiobiological EQD_2 per fraction converted from the corresponding physical dose of an i^{th} arbitrary voxel. All the $BED_{voxel}\ (i)$ and $EQD_{2,\,voxel}\ (i)$ voxels were used to reconstruct the EQD_2-and BED-Cube having the same dimensions as that of the physical Dose-Cube. In this program, there are two options–one for special priority to OARs radiobiology and the other one is for special priority to tumor radiobiology. Otherwise, there is the possibility of misinterpretation for tumor and OARs radiobiology. In the OARs radiobiology priority case, the whole contours of OARs were considered for BED-and EQD_2-colorwash, iso-BED and iso-EQD_2 curves calculation of OARs and the overlapping regions of OARs with PTV were excluded from BED-and EQD_2-Cube calculation of PTV for BED- and EQD_2-colorwash, iso-BED, and iso-EQD_2 curves display. In the tumor radiobiology priority case, the whole contours of PTV were considered for BED-and EQD_2-colorwash, iso-BED and iso-EQD_2 curves calculation of PTV and subsequent display on CT image dataset. PTV and OARs overlapping region were excluded from BED-and EQD_2-colorwash, iso-BED, and iso-EQD_2 curves display of OARs.

Reconstruction of BED- and EQD_2-volume histograms

For the reconstruction of BED-and EQD_2-volume histograms from the physical Dose-Cube, voxels indices of each contoured structure were searched in the Structures-Cube and then mapped to the physical Dose-Cube for extraction of doses corresponding to the searched voxels. Frequency distribution of voxels inside each contoured structure having the same doses was calculated. Physical doses of these voxels were converted into BED and EQD_2 using mathematical equations (1) and (2), respectively. Further, BED and EQD_2 based differential DVH and cumulative DVH were generated from the frequency distribution of doses inside each contoured structure.

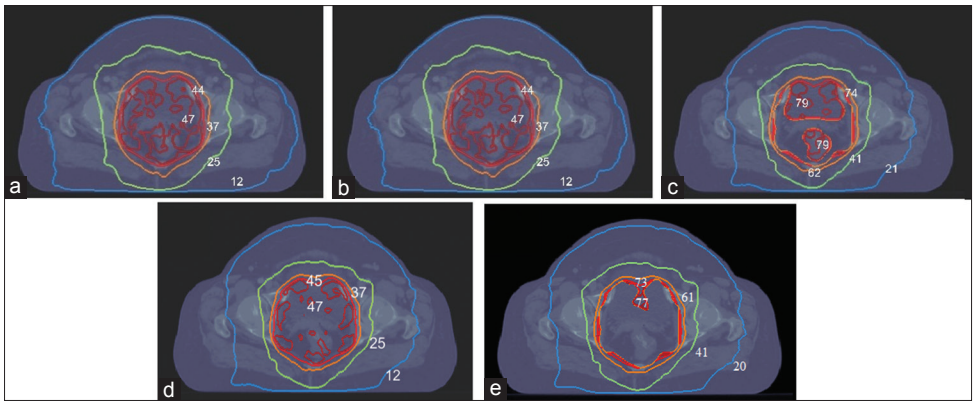

Figure 2: Absolute physical isodose (a), iso-EQD_2 (b) and iso-BED (c) curves display with special priority given to OARs radiobiology and iso-EQD_2 (d) and iso-BED (e) displays with special priority given to PTV radiobiology over the same axial slice of the CT-Cube

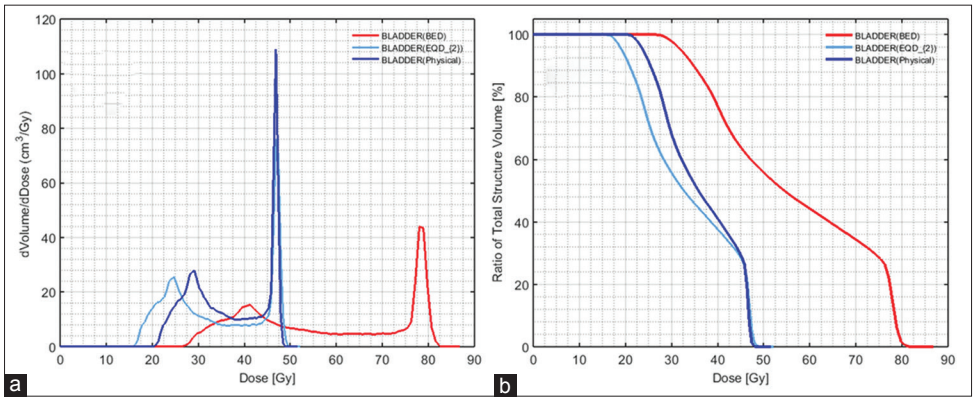

Figure 3: Comparison of reconstructed differential (a) and cumulative (b) physical dose, EQD_2-and BED-volume histogram of bladder organ (OARs) with special priority given to OARs radiobiology

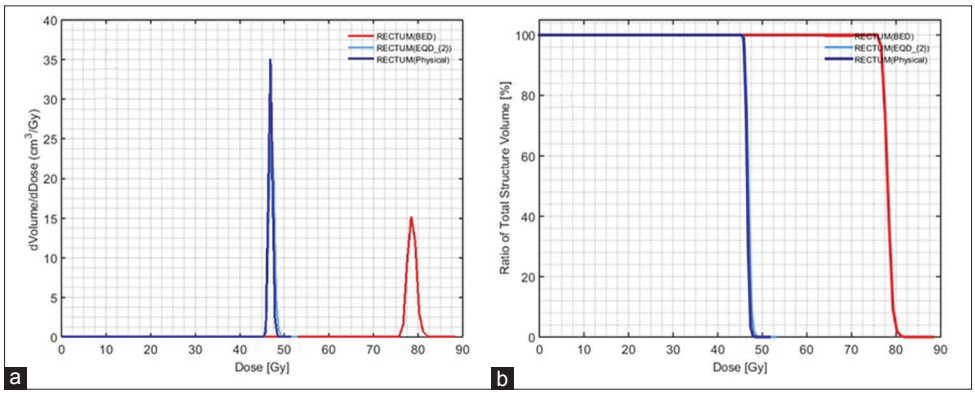

Figure 4: Comparison of reconstructed differential (a) and cumulative (b) physical dose, EQD_2-and BED-volume histogram of rectum organ (OARs) with special priority given to OARs radiobiology

Results and Discussion

Figure 1 shows the physical dose, EQD_2-and BED-colorwash display on the same axial, sagittal slice of CT-Cube and Structures-Cube reconstructed from the exported DICOM-RT files containing the information of the treatment plan of carcinoma cervix patient. The maximum dose in the physical dose colorwash [Figure 1a and b], EQD_2-colorwash [Figure 1c and d] and BED-colorwash [Figure 1e and f] was 49.10 Gy, 49.65 Gy, and 82.67 Gy, respectively, for priority given to OARs radiobiology. Similarly, for priority given to tumor radiobiology, the maximum dose of EQD_2-colorwash [Figure 1g and h] and BED-colorwash [Figure 1i and j] was 49.65 Gy and 81.23 Gy, respectively. Slice-by-slice dose evaluation and DVHs based evaluation are most widely used methods for the analysis of the treatment plan.[4] Both the evaluation methods have been modified in our present work.

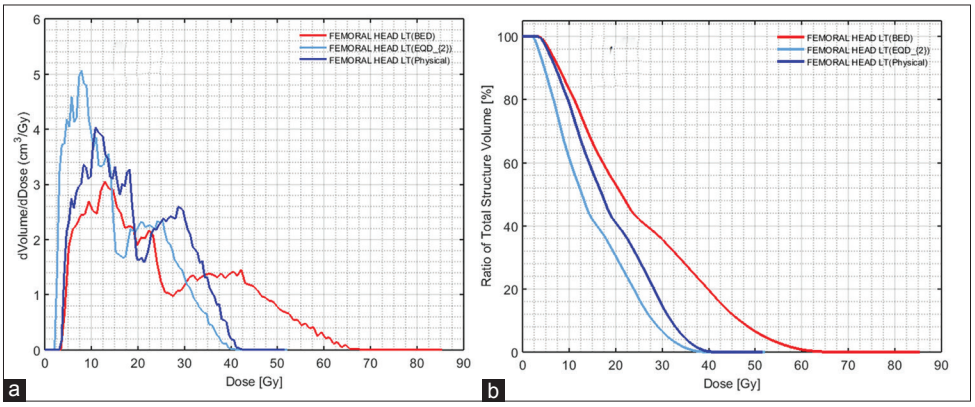

Figure 5: Comparison of reconstructed differential (a) and cumulative (b) physical dose, EQD_2 and BED-volume histogram of left femoral head (OARs) with special priority given to OARs radiobiology

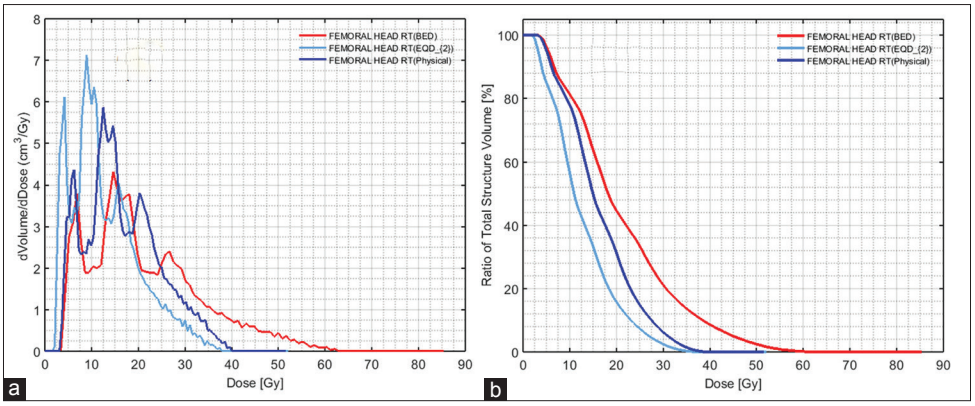

Figure 6: Comparison of reconstructed differential (a) and cumulative (b) physical dose, EQD_2-and BED-volume histogram of right femoral head (OARs) with special priority given to OARs radiobiology

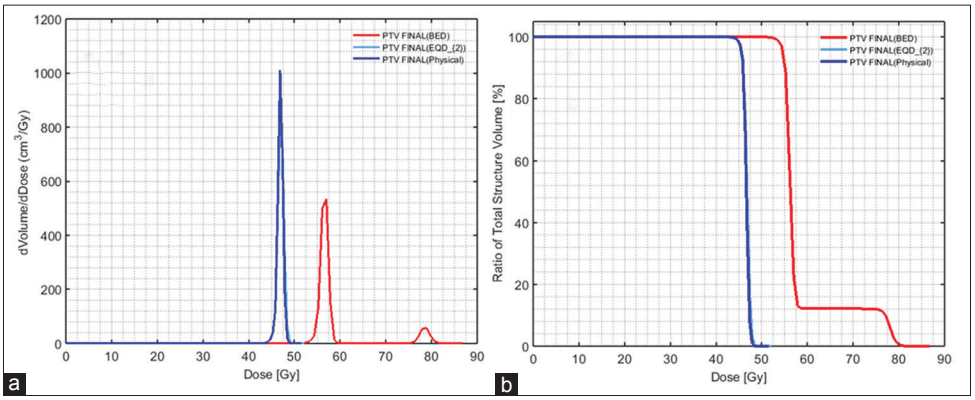

Figure 7: Misinterpretation of reconstructed differential (a) and cumulative (b) physical dose, EQD_2-and BED- volume histogram of planning target volume (target volume) when special priority given to OARs radiobiology

First, TPS displays the dose colorwash and isodose curves regarding physical dose, but we have added the radiobiological equivalent BED-and EQD_2-colorwash [Figure 1], iso-BED and iso-EQD_2 curves [Figure 2] displays. Second, BED- and EQD_2-volume histograms were reconstructed from the BED- and EQD_2-Cube and compared with the physical DVHs of the different organs and target volumes which are useful for evaluating the treatment plans on the basis of tissues-and tumor-specific radiobiological parameters. In this study, the effect of fraction size was also considered by incorporating the tissue-specific radiosensitive parameter (α/β) for the BED and EQD_2 based evaluation.[10] In this carcinoma cervix case, rectum was completely overlapped with the PTV, the bladder was partially overlapped with the PTV and left and right femoral head was very close to the PTV as shown in axial and sagittal views of Figure 1. Those volumes overlapped with the PTV showed the higher hotspot volumes of BED-colorwash as compared to those of non-overlapped region of PTV due to

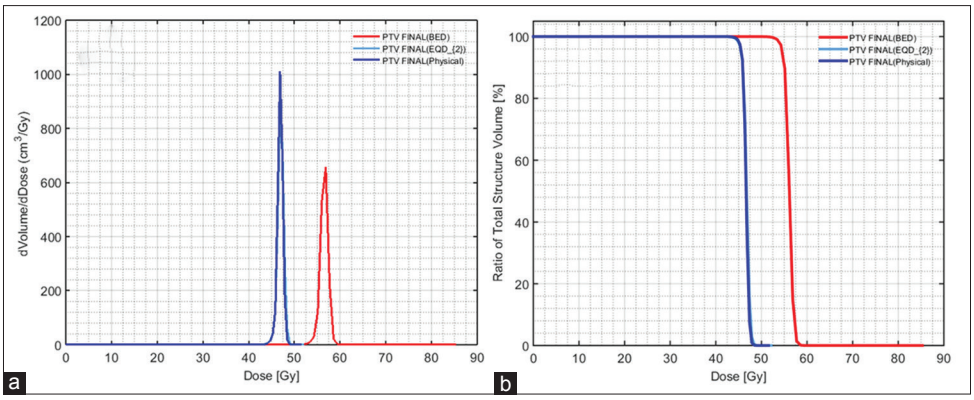

Figure 8: Comparison of reconstructed differential (a) and cumulative (b) physical dose, EQD_2-and BED-volume histograms of PTV (target volume) with special priority given to PTV radiobiology

the uses of lower values of α/β (3 Gy) of rectum and bladder and higher values of α/β (10 Gy) of PTV, respectively, when the plan evaluation priority was given to OARs radiobiology. These higher value hotspot regions of bladder and rectum are the important regions for the critical review and evaluation of RT treatment plans. In the second case, when priority was given to PTV radiobiology, entire PTV volume was assigned the value of 10 Gy to α/β and excluded the overlapped volumes from OARs volume as shown in Figure 1g-j. BED-and EQD_2-colorwash [Figure 1g-j] show significant changes in hotness region of bladder and rectum when compared to EQD_2-, and BED-colorwash [Figure 1c-f] obtained from the case when priority was given to OARs radiobiology. EQD_2- and BED-colorwash [Figure 1g-j] obtained in this case gives correct information of radiobiological doses of PTV, but misinterpret the radiobiological doses of OARs because of higher priority given to PTV voxels overlapped with OARs, but in the case of OARs radiobiology priority, radiobiological doses of OARs were correctly interpreted and whereas PTV radiobiological doses were misinterpreted. When the priority of PTV radiobiology was selected, surrounding normal tissues BED-colorwash was hotter than PTV BED-colorwash as shown in Figure 1i-j.

Similarly, Figure 2 displays 95%, 90%, 75%, 50%, and 25% iso-dose and iso-effective curves of the maximum value of the physical, EQD_2 and BED dose distribution on the same axial slice. Figure 2a shows the physical iso-dose curves, and Figure 2b and c show the iso-EQD_2 and iso-BED curves, respectively, with special priority given to OARs radiobiology and Figure 2d and e show the iso-EQD_2 and iso-BED curves with the special priority given to PTV radiobiology, respectively. These figures show the changes in the values of iso-BED and iso-EQD_2 curves and hence in the hotness of BED-and EQD_2-colorwash as compared to that of physical dose colorwash as shown in Figure 1. The areas enclosed by the lower iso-EQD_2 and iso-BED curves were relatively smaller as compared to those of physical iso-dose curves [Figure 2] because of the impact of tissue-specific parameter (α/β =3). In case of the voxels enclosed by the target volume, the value of α/β ratio was assigned 10 Gy, whereas that of the voxels of the OARs were assigned 3 Gy. So when the priority is chosen for OARs radiobiology, 79 Gy iso-BED curves enclose the bladder and rectum regions overlapped with PTV volume in Figure 2c which is not observed when PTV radiobiology mode is selected [Figure 2e]. In case of iso-EQD_2 curves in Figure 2b and d, there are not gross changes in iso-EQD_2 curves due to renormalization of BED-Cubes for both PTV (α/β = 10 Gy) and OARs ([α/β] = 3 Gy) by the corresponding relative effectiveness (1 + 2/[α/β]) of PTV and OARs in between the selections of the two modes. The same were observed in Figure 1 also. In Figure 2e, iso-BED region of PTV is enclosed by higher iso-BED curves of OARs (bladder and surrounding normal tissue regions) in tumor radiobiology mode

Figures 3-8 show the changes in BED-and EQD_2-volume histograms (both differential and cumulative) of bladder, rectum, left and right femoral head (OARs) and PTV. There were shifts in all BED-and EQD_2-volume histograms of all the OARs and PTV. When the OARs radiobiology mode is selected, a few percentage volume of PTV region overlapped with OARs were observed shifted for PTV BED-volume histogram due to the geometrical inclusion of a few region of rectum and bladder which are of lower tissue specific parameter (α/β = 3 Gy) different from that of PTV as shown in Figure 7. This will produce misinterpretation in PTV radiobiology analysis while using OARs radiobiology mode. When the PTV radiobiology mode is selected ignoring the radiobiology of OARs, the above percentage value of PTV region is not shifted in PTV BED-volume histogram as the whole volume of PTV were assigned α/β values of 10 Gy [Figure 8]. PTV EQD_2-volume histograms were not shifted from those of physical DVHs [Figures 7 and 8], because the voxels inside the PTV received the dose in the range from 95% to 107% of the prescribed dose of 2 Gy/fraction. Voxels outside the PTV did not receive the same dose per voxel due to rapid dose fall outside the PTV. Voxels of the OARs overlapped with PTV showed a significant increase in the overall BED of the OARs volume due to homogeneous dose of PTV. OARs voxels near and outside the PTV received the lesser doses than that of prescribed dose per fraction (i.e. 2 Gy/fraction) due to increase in distance from the PTV boundary. Hence the values of the

EQD_2-volume histogram were observed lesser than that of the physical dose because in EQD_2 formalism, 2 Gy normalization factor was used, while the BED values of the voxels increased due to quadratic term in BED calculation. The changes in BED-and EQD_2-volume histograms of OARs are shown in Figures 3-6.

Conclusion

The present study uses the voxel-based approach for evaluation of the quality of RT treatment plans. Voxel-based conversion of physical Dose-Cube into BED-and EQD_2-Cube and subsequent reconstruction of physical dose-, BED-and EQD_2-volume histograms provides additional information for evaluation of RT treatment plan. Physical dose colorwash, isodose curves, and DVHs were compared with the BED-and EQD_2-colorwash, iso-BED, and iso-EQD_2 curves and BED-and EQD_2-volume histograms, respectively, which incorporate the effect of fraction size and number of fractions. This work utilizes the tissue specific radiobiological parameter such as α/β ratio and number of fractions of different dose fractionation scheme. However, physical DVHs, dose colorwash and isodose curves do not contain the effect of radiosensitivity parameters (dose per fraction, number of fraction, α/β ratio, etc.) whereas BED-and EQD_2-colorwash, BED-and EQD_2-volume histograms, and iso-BED and iso-EQD_2 curves directly incorporate these radiosensitivity parameters. The proposed evaluation method in the current study describes supplementary radiobiological recipes (BED and EQD_2 based dose colorwash, isodose curves, and DVHs) along with the existing methods. The given method of evaluation will be very helpful while taking decision to finalize a treatment plan by radiation oncologists and clinical medical physicists during evaluation and approval of RT treatment plan.

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Conflicts of interest

There are no conflicts of interest.

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