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Dosiomics-based comparison of dose distributions in nasopharyngeal cancer patients: 3D-CRT versus Tomotherapy

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► ***Original article***

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ABSTRACT

Background: This research was conducted to compare dosiomics features extracted from planning target volume (PTV) between the two three-dimensional conformal radiation therapy (3D-CRT) and helical tomotherapy (HT) techniques in nasopharyngeal cancer. ***Materials and Methods:*** 3D-CRT plans were designed for ten nasopharyngeal patients previously treated with HT. For both treatment techniques, the total prescription dose was 70 Gray in 33 fractions. At first, the dosimetric parameters, including mean dose, conformity index (CI), and homogeneity index (HI), were calculated for two techniques. Then, using 3D-Slicer software, dosiomics features were extracted from the dose matrix of PTV. ***Results:*** In comparing the plans regarding dosimetric parameters, HT plans had a lower mean dose and higher CI (p-value <0.01 and <0.001, respectively). HI had no statistically difference between the two groups (p>0.9). Among 93 features extracted from PTV70, only 40 features including eight features from the first-order group, ten features from the gray-level co-occurrence matrix group (GLCM), seven features from the gray-level dependence matrix group (GLDM), ten features from the gray-level run-length matrix group (GLRLM), four features from the gray-level size-zone matrix group (GLSZM), and one feature from the neighboring gray-tone difference matrix group (NGTDM) were found to be significantly different between the two groups. ***Conclusion:*** According to the results, the dosiomics features can distinguish the differences between dose distributions in different studied plans. However, more studies should be done in selecting the most suitable features for use in evaluating the quality of the treatment plans.

INTRODUCTION

Currently, treatment plans in radiation oncology are often optimized and evaluated based on dose-volume histogram (DVH), and other factors related to planning are not considered [1]. Dosimetric factors such as $V_{D\%}$ (volume exposed to dose equal to or higher than D Gray) and $D_{V\%}$ (the dose received by V percent of volume) use only partial information in the dose distribution. They are calculated based on DVHs [1, 2]. However, a known limitation of DVH-based dosimetric factors is that it incorporate a three-dimensional dose distribution into a two-dimensional curve and loses spatial information of 3D dose distribution. It may not be sufficient to predict radiation complications. DVH may not always provide sufficient data from the dose distribution or may not distinguish slight differences in the dose distribution [3]. Another method of evaluating patients' plans is based on normal tissue complication probability (NTCP) and tumor control probability (TCP) models. NTCP models, converting the entire DVH curve into a single parameter, use all the information of the DVH curve and have better prediction capabilities than dosimetric factors [2].

However, due to the lack of spatial information in DVH, plans with different dose characteristics may result in the same DVH curve and, subsequently the same NTCP value [2, 4]. In addition, dose-volume parameters and patient-related clinical factors include the main structure of current models [5]. The current models have been obtained using the data of patients of one or several centers despite the different conditions of the patients and the different types of complications. These models cannot fully explain the response to treatment outcomes and the complications caused by radiation among people [6]. Therefore, introduction of new factors to investigate patient-specific responses to radiation therapy, optimization of TCP models, and better evaluation of calculated dose distributions in planning are needed. Recently, in studies related to radio-oncology and medical physics, to purposefully determine the relationship between the personal information of the patient and the outcome of the treatment, the use of spatial characteristics of patient-specific medical images under the name of radiomics features or imaging biomarkers is one of the most interesting methods introduced in targeted therapy [7, 8]. The extraction of radiomics features from the image

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allows the conversion of different image modalities into powerful quantitative data and the identification of correlations between voxels.

Radiomics can provide rich information about tumors or normal tissue and can also be used to build predictive or prognostic models [1, 5, 7, 9-14]. Recently, a new method called dosiomics, derived from the radiomics method, has attracted the attention of researchers in this field [8]. Dosiomics features are extracted from the dose matrix instead of medical images [10] to obtain information about the correlation of voxels on dose distribution. The dosiomics features allow a better description of the dose distribution than DVHs [3, 4, 8, 9, 15]. Integrating dosiomics with DVH can be an advanced tool for evaluation of radiotherapy treatment planning. Dosiomics features can improve the performance of NTCP and TCP models. Several studies have been conducted to compare the dosimetric and radiobiological factors of modern radiation therapy methods and the three-dimensional conformal radiation therapy (3D-CRT) method [16–22]. Also, recently, it has been proved that the dosiomics features can work better than the factors based on DVH and NTCP, as factors for the prognosis and prediction of damage caused by radiation therapy [2, 3, 8, 10, 15].

Nevertheless, it seems that according to the results of recent research to improve the performance of dosiomics features compared to DVH-based factors in predicting treatment outcomes, these new dosiomics features can be used in the future along with DVH factors to evaluate treatment plans. Until now, there is no reported study on comparing a dosiomics-based 3D dose distribution in patients with nasopharyngeal cancer treated by helical tomotherapy (HT) and 3D-CRT techniques. Therefore, the purpose of this study was dosimetric and dosiomics-based comparison of treatment planning between 3D-CRT and HT techniques in nasopharyngeal cancer patients.

MATERIALS AND METHODS

Patient characteristics and CT simulation

Ten retrospective patients with nasopharyngeal cancer (NPC) treated with HT in our hospital (Seyed Alshohada Hospital, Isfahan, Iran) between December 2021 and December 2023 were selected for this research. A summary of patients' information is given in table 1. All patients were immobilized in the supine position to obtain a 3 mm slice thickness CT images using a SOMATOM Definition AS or SOMATOM Confidence CT scanner (Siemens, Germany).

Target delineation

All CT images were imported to the Precision treatment planning system (TPS) (Accuray, USA, version 2.0.1.1) for contouring. Clinical target volume (CTV_{70}) was defined as gross tumor volume (GTV_{70}) and highly positive lymph nodes (GTV_{nd}) as any lymph nodes >1 cm or nodes with necrotic cancer. $CTV_{59.4}$ was delineated as the area at high risk of microscopic involvement. PTV_{70} and $PTV_{59.4}$ was defined as CTV_{70} and $CTV_{59.4}$ with a margin of 3 mm. Also, PTV-node was defined as neck lymph nodes. Figure 1 shows the image of an axial cut of a patient and the contouring of the target volume.

Table 1. Clinical information of patients.

Patients	Sex	Age		Pathology	Clinical stage	AJCC prognostic stage groups
P 1	Male	15	Average: 46	Metastatic SCC	Tx N2	Stage Ш
P 2	Male	39		Undifferentiated Carcinoma	T2 N2	Stage Ш
P 3	Male	47		Metastatic Carcinoma	T3 N2	Stage Ш
P 4	Female	69		SCC	T1 N2	Stage Ш
P 5	Female	64		Poorly Differentiated Carcinoma	T1 N2	Stage Ш
P 6	Male	43		Non Keratinizing Carcinoma	T1 N2	Stage Ш
P 7	Male	35		Undifferentiated Carcinoma	T2 N1	Stage П
P 8	Male	52		Not Available	Not Available	Not Available
P 9	Female	36		Non Keratinizing SCC	T2 N3	Stage IVA
P 10	Male	58		Carcinoma	T1 N1	Stage П

Abbreviations: AJCC: American Joint Committee on Cancer.

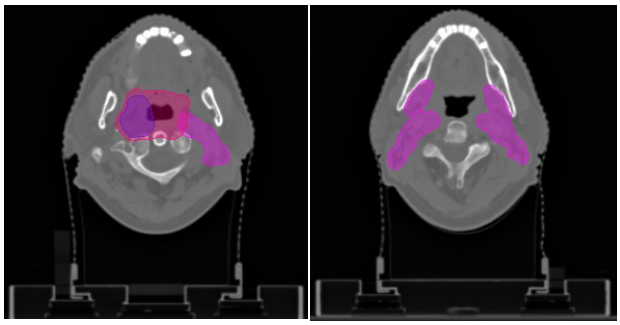


Figure 1. Target volumes delineated by the physician as defined in the method section. Pink: PTV-node (in the right), red: PTV-59.4 (in the left), blue: PTV-70 (in the left)

Planning techniques and prescribed dose 3D-CRT plans

Treatment planning for 3D-CRT were performed using the TIGRT TPS (Lina Tech – Treatment Planning System, version: 1.0.10.573, USA), for execution using a Siemens Primus equipped with a 6 MV photon beam (Siemens, Germany). The plans were designed to deliver the dose in two steps: in the first step, a prescribed dose of 59.4 Gy in 33 fractions for the PTV_{70}, PTV-node, and $PTV_{59,4}$, and in the second step, a dose of 10.6 Gray was considered as a

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boost for the PTV_{70} in 10 fractions, which covered more than 95% of PTV_{70} volume. In practice, the prescribed dose of 70 Gy to the primary tumor and 59.4 to the high-risk areas and the neck lymph nodes is not applicable in the 3D-CRT method. Nevertheless, we wanted the dosiomics features extracted from the dose distribution to be independent of the total prescribed dose and only the treatment modality and, subsequently the type of TPS to be influential in the dose matrix calculations. To solve that issue, the prescription dose was considered the same in both treatment techniques. The plans were designed using two lateral parallel opposed beams for the head and two parallel opposed anterior/posterior beams for the neck. The match line of beams was made by giving an angle to the couch for lateral beams. An example of 3D-CRT planning for a patient is shown in figure 2.

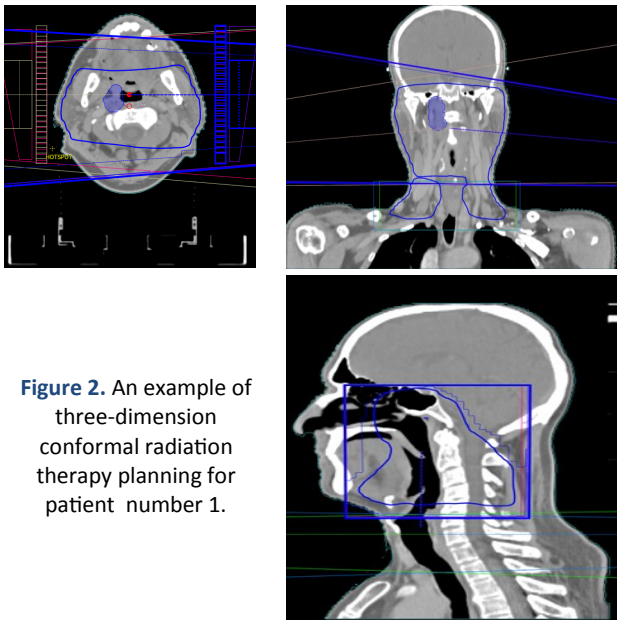


Figure 2. An example of three-dimension conformal radiation therapy planning for patient number 1.

HT plans

Treatment planning of HT was performed using the Precision TPS (Accuray Precision 2.0.1.1, USA). Three main parameters were set by the operator: field width 2.5-5 cm, pitch 0.434-0.440, and modulation factor 3-3.8. A Convolution-Superposition algorithm was used for dose calculation with a grid size of (X, Z): 0.8-0.98 and (Y): 2-5 mm. The prescribed dose for $PTV_{59,4}$ and PTV-node was 59.4 Gy, and a simultaneously boosting dose for PTV_{70} was 70 Gy.

Dosimetric investigation and extraction of dosiomics features

At first, for the dosimetric evaluation of plans, the parameters such as mean dose, homogeneity index (HI), and conformity index (CI) [16,20] for PTV_{70} were obtained for two treatment methods. The CI was used to assess the conformity of the dose distribution. The CI is defined according to the equation 1:

$$CI = \frac{V_{t,ref}}{V_t} \times \frac{V_{t,ref}}{V_{ref}} \quad (1)$$

$V_{t,ref}$, V_t, and V_{ref} represent the volume of the target that received the prescribed dose, the target volume, and the total volume that received the prescribed dose, respectively. According to the range of 0 to 1 for CI values, the higher the CI value, the higher the conformity of the dose to the target. HI was calculated using the equation 2:

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}} \quad (2)$$

Where $D_{98\%}$, $D_{50\%}$, and $D_{2\%}$ represent the dose received by 98%, the dose received by 50%, and the dose received by 2% of the PTV volume. HI was used to assess the homogeneity of the dose distribution. The lower the value of HI means the dose distribution has good homogeneity for the target volume.

Then, using the SlicerRadomics module (a Python scripted loadable module bundled in the SlicerRadomics extension) in 3D Slicer [23], a total of 93 dosiomics features were extracted from the PTV70 for each of the 3D-CRT and HT plans. The different families of extracted dosiomics features from area of PTV_{70} included first-order dosiomics features of the dose matrix (18 features) and 75 texture features (including the Gray Level Co-occurrence Matrix (GLCM) (24 features), Gray Level Dependence Matrix (GLDM) (14 features), Gray Level Run Length Matrix (GLRLM) (16 features), Gray Level Size Zone Matrix (GLSZM) (16 features), and Neighborhood Gray Tone Difference Matrix (NGTDM) (5 features). The dosiomics features used in this research have already been explained in references [1,3]. 3D-Slicer software version 5.3.0 was used to extract the features of dosiomics. To extract the features after treatment design, CT images and 3D dose matrix in DICOM format were exported from TPSs and imported into 3D Slicer software. Before the extraction of dosiomics features, 1×1×1 mm^3 resampling was performed for all dose distributions. Then, the discretization of the resampled dose distribution between the minimum and maximum dose was performed with a fixed bin width of 1 Gray. An overview of the study is given in figure 3.

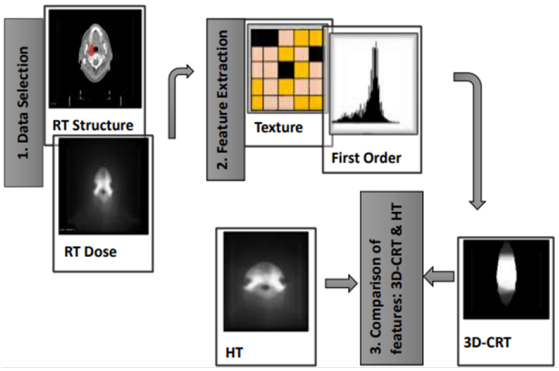


Figure 3. Overall workflow of the study. Abbreviations: HT = Helical Tomotherapy; 3D-CRT = Three-dimensional Conformal Radiotherapy.

Statistical analyzes

To compare dosimetric factors and dosiomics

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features of 3D-CRT plans versus HT, paired *t-test* and Wilcoxon statistical tests were performed for parametric and non-parametric data, respectively. A P-value<0.05 was considered statistically significant. IBM SPSS version 19.0 software was used to perform all statistical analyses (SPSS, Inc., Chicago, IL, USA).

RESULTS

The plans of 10 patients with NPC were designed using TIGRT and Precision TPSs. Compared with 3D-CRT plans, HT plans showed superior CI (p<0.001). 3D-CRT and HT plans had mean doses to PTV of 71.5 ± 0.7 Gray and 70.1 ± 1.3 Gray, respectively (p<0.01). In addition, for 3D-CRT and HT plans, CI and HI were 0.12 ± 0.06, 0.77 ± 0.12 (p < 0.001), and 0.1 ± 0.03, 0.1 ± 0.03 (p > 0.937), respectively. Figure 4 shows the logarithmic diagram for comparing the mean values of 93 dosiomics features extracted from 3D-CRT and HT plans; among the 93 features extracted from PTV_{70}, only 40 features (including: seven features from the first-order group, ten features from the GLCM group, seven features from the GLDM group, ten features from the GLRLM group, four features from the GLSZM group, and one feature from the NGTDM group) were found to be significantly different between the two groups. Table 2 shows the information related to the statistically significant results of the features mentioned above. Only the features with a statistical difference between the two groups are reported in this table. Also, figure 5 shows the difference in dose distribution between plans 3D-CRT and HT.

Table 2. The values of dosiomics features extracted from 3D-CRT and HT plans (only the features that are statistically significantly different between the two radiotherapy techniques).

	3D-CRT	HT	P-Value	
Dosiomics Features Name	**Mean ±SD**	**Mean ±SD**	**paired t-test**	**Wilcoxon**
First order group				
10Percentile	69.48±0.84	67.84±1.64	0.004	--
90Percentile	74.11±1.13	71.96±1.03	0.000	0.007
Energy	$(0.77\pm0.99)\times10^{9}$	$(0.73\pm0.93)\times10^{9}$	0.058	0.007
Maximum	79.97±6.58	75.22±1.74	0.029	0.012
Mean	71.73±0.68	70.18±1.15	0.001	0.007
Median	71.81±0.75	70.58±1.1	0.006	0.017
RootMeanSquared	71.76±0.7	70.2±1.14	0.001	0.007
TotalEnergy	$(0.77\pm0.99)\times10^{9}$	$(0.73\pm0.93)\times10^{9}$	0.058	0.007
GLCM group				
Correlation	0.92±0.03	0.86±0.07	0.044	0.047
DifferenceAverage	0.3±0.16	0.47±0.08	0.007	0.012
DifferenceEntropy	0.9±0.28	1.2±0.12	0.003	--
Id	0.87±0.03	0.78±0.03	0.000	--
Idm	0.87±0.03	0.77±0.03	0.000	--
Idn	0.98±0.00	0.97±0.01	0.001	--
Imc1	-0.62±0.04	-0.41±0.06	0.000	0.005
Imc2	0.98±0.01	0.91±0.06	0.006	0.005
InverseVariance	0.21±0.03	0.36±0.05	0.000	0.005
MCC	0.95±0.01	0.88±0.07	0.011	0.005
GLDM group				
DependenceNonUniformity	$(13.77\pm16.21)\times10^{3}$	$(69.9\pm87.93)\times10^{2}$	0.018	0.005
DependenceNonUniformityNormalized	0.1±0.02	0.04±0.00	0.000	0.005
GrayLevelNonUniformity	$(21.01\pm22.53)\times10^{3}$	$(28.17\pm30.47)\times10^{3}$	0.059	0.028
LargeDependenceEmphasis	412.75±33.32	282.12±48.19	0.000	--
LargeDependenceLowGrayLevelEmphasis	15.3±17.59	3±5.04	0.038	0.028
LowGrayLevelEmphasis	0.03±0.04	0.01±0.01	0.056	0.047
SmallDependenceLowGrayLevelEmphasis	0.00±0.00	0.00±0.00	0.237	0.047
GLRLM group				
GrayLevelNonUniformity	$(54.72\pm56.23)\times10^{2}$	$(94.16\pm102.22)\times10^{2}$	0.025	0.005
LongRunEmphasis	33.08±10.09	11.29±3.71	0.000	0.005
LongRunHighGrayLevelEmphasis	$(264.88\pm92.23)\times10^{2}$	$(40.34\pm41.73)\times10^{2}$	0.080	0.047
LongRunLowGrayLevelEmphasis	1.32±1.68	0.13±0.25	0.046	0.022
RunEntropy	5.83±0.38	4.87±0.37	0.000	--
RunLengthNonUniformity	$(130.8\pm92.23)\times10^{2}$	$(24.97\pm32.89)\times10^{3}$	0.011	0.005
RunLengthNonUniformityNormalized	0.2±0.06	0.35±0.05	0.000	--
RunPercentage	0.29±0.04	0.44±0.05	0.000	--
RunVariance	14.39±3.6	5.61±2.07	0.000	0.005
ShortRunEmphasis	0.39±0.11	0.6±0.05	0.000	--
GLSZM group				
GrayLevelNonUniformity	54.23±96.46	118.43±108.42	0.004	0.005
GrayLevelNonUniformityNormalized	0.1±0.06	0.16±0.06	0.021	--
LargeAreaHighGrayLevelEmphasis	$(922.33\pm92.23)\times10^{2}$	$(14.63\pm20.18)\times10^{2}$	0.048	0.005
LargeAreaLowGrayLevelEmphasis	$(922.33\pm92.23)\times10^{2}$	$(174\pm92.23)\times10^{2}$	0.074	0.047
NGTDM group				
Coarseness	$0.5\times10^{-3}\pm0.00$	$0.3\times10^{-3}\pm0.00$	0.025	0.007

Abbreviations: 3D-CRT: Three-Dimension Conformal Radiation Therapy, HT: Helical Tomotherapy, SD: Standard Deviation, GLCM: Gray Level Co-occurrence Matrix, GLDM: Gray Level Dependence Matrix, GLRLM: Gray Level Run Length Matrix, GLSZM: Gray Level Size Zone Matrix, NGTDM: Neighborhood Gray Tone Difference Matrix. Other information about the names of each feature is referenced in the previous articles in the method section.

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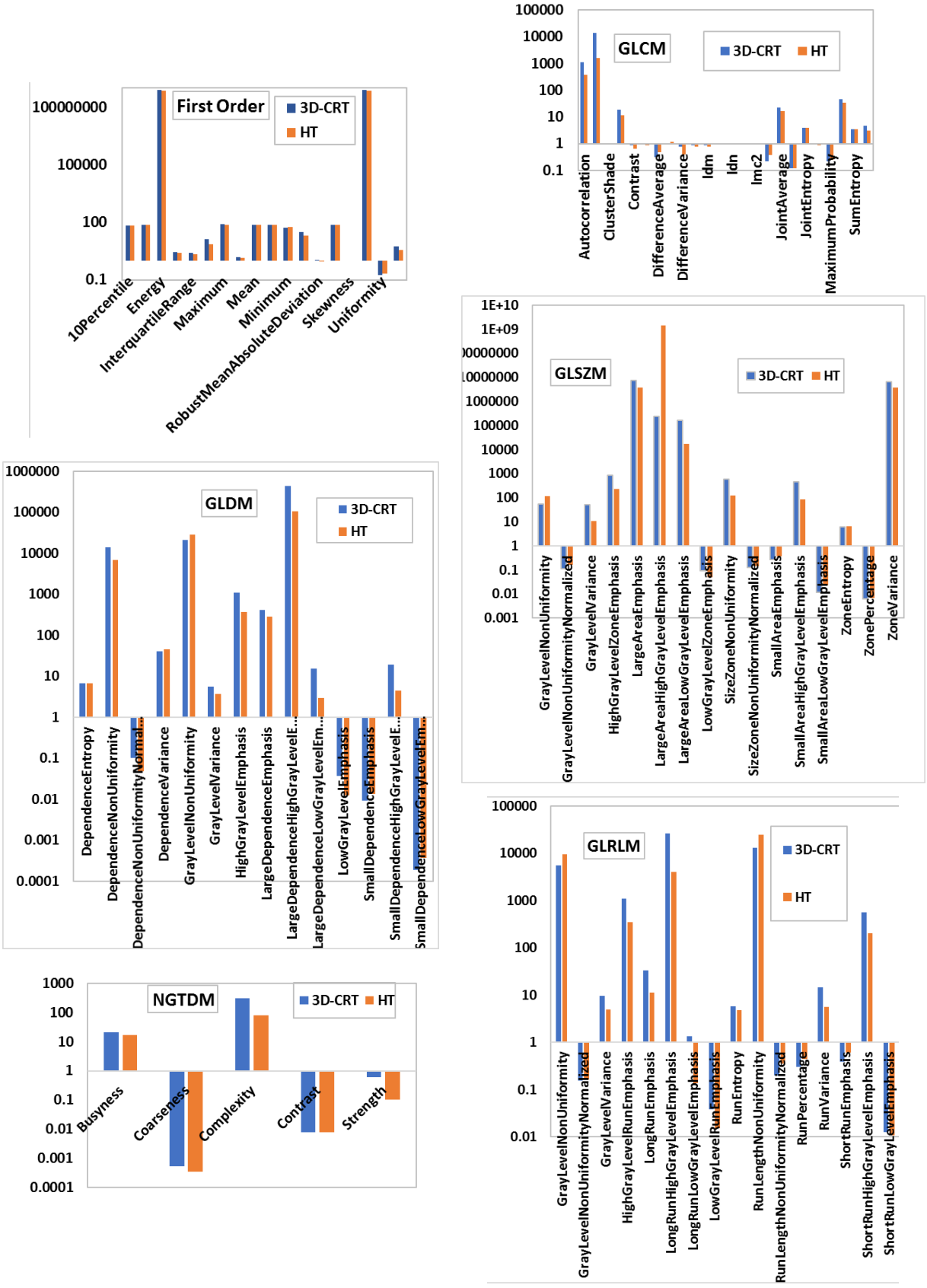


Figure 4. An overview of the comparison of all dosiomics features. Abbreviations: Gray Level Co-occurrence Matrix (GLCM), Gray Level Dependence Matrix (GLDM), Gray Level Run Length Matrix (GLRLM), Gray Level Size Zone Matrix (GLSZM), and Neighborhood Gray Tone Difference Matrix (NGTDM);

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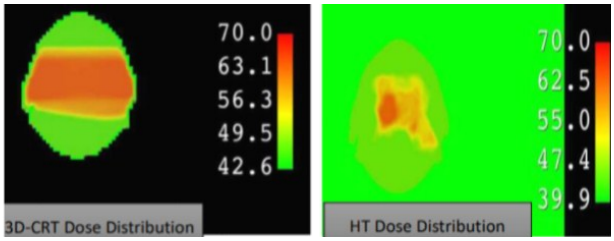


Figure 5. A view of difference in the dose distribution of three-dimension conformal radiation therapy and helical tomotherapy.

DISCUSSION

In the last decade, the use of dosiomics features was introduced as an option to improve the evaluation of treatment plans and the prediction of treatment outcomes [2,3,8,15]. Several studies have been conducted on the limitations of dosimetric factors extracted from DVH [1,2]. Dosiomics features extraction is a new method for three-dimensional investigation of dose distribution in the radiotherapy treatment planning. The extraction of dosiomics features from the dose matrix considers complex spatial information for the designed plans, which is not present in the DVH-based dosimetric factors [8].

In this research, in addition to comparing dosimetric factors, we examined and compared 93 dosiomics features extracted from PTV in plans designed for 3D-CRT and HT. Until now, no study has been done to compare the dosiomics features between plans designed for different radiation therapy techniques.

Nevertheless, some studies have been conducted on the ability of dosiomics features to predict treatment outcomes after radiation therapy. In the study of Wu *et al.* [15], by investigating whether dosiomics can be helpful in predicting local recurrences (LR) of patients with NPC treated with IMRT, they have shown that dosiomics can be helpful in predicting LR. According to table 2, five of the dosiomics features (First order: 90th percentile, GLRLM: Long Run Low Gray Level Emphasis, GLDM: Large Dependence Low Gray Level Emphasis and Low Gray Level Emphasis, GLSZM: Large Area Low Gray Level Emphasis) reported with significant differences are the same as the features noted in Wu study. Another study by Murakami *et al.* [1] has been conducted to investigate the dosiomics features in predicting biological recurrence after prostate radiation therapy. Despite the difference in the type of disease in present study and their study (NPC versus prostate cancer), none of the features reported in table 2 were consistent with their study [1]. Also, several studies have been conducted on dosiomics as a parameter for predicting radiation damage to normal tissue. For example, some studies for predicting lung pneumonia [2, 3, 8] and one study for predicting hypothyroidism [4] have used dosiomics features. These studies have examined the features obtained from normal tissue. However, the three features given in table 2 are consistent with the results of their research (First order: 90th percentile, GLRLM: RunEntropy and RunLengthNonUniformityNormalized) [4, 8].

It seems that dosiomics features with significant differences in our research can detect the difference in 3D dose distribution between the two techniques. Of course, it should be pointed out whether the reason for the difference is only the differences resulting from the different treatment techniques and TPS. That is why several studies have been carried out in investigating the stability and reproducibility of features against some parameters influencing the extraction of dosiomics features. For example, stability studies have been done against the types and versions of dose calculation algorithms [24], calculation grid size [25], radiation therapy techniques and modalities, and different treatment planning systems [26]. According to the results of these studies, the textural features have the most variability, especially in target volume compared to other region of interests. In consistent with this studies, the highest number of features with significant differences in the two groups were: GLCM and GLRLM (10 times), GLDM and First-Order (7 times), GLSZM (4 times), and finally NGTDM (1 times). Of course, in this work, only the difference of dosiomics features between the two methods was evaluated, and the variability of the features were not investigated.

CONCLUSION

According to the results of our study, some dosiomics features have the ability to distinguish dose distribution between different plans. It seems that more studies in this field may lead to the introduction of some of these dosiomics features as factors for evaluating and comparing treatment planning quality. Of course, before doing this, it is necessary to check the extraction of dosiomics features in terms of stability and other issues to select the appropriate dosiomics features for use.

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