Reviewer #1: In the study the authors aim to create a neural network to predict DVH starting from the dose information of individual conformal beams for knowledge-based planning.
They start from the consideration that for complex cases such as nasopharyngeal carcinomas the use of simple anatomical information such as the distance of the OARs from the PTV surface is not sufficient to accurate predict the DVH, but further information such as the treatment beam orientation are required.
Once predicted the DVH using the model elaborated, the DVH will be used to calculate the equivalent uniform dose (EUD) and new VMAT plans will be calculated considering the EUD as dose constraints.
The new plans (EP) have been then compared with the clinical plans (CP) and the authors found better consistency and lower doses to OARs.
Although the topic is of interest and the work done interesting, I believe that the present work is not written in a clear manner and it results difficult to follow.
It contains several grammar errors and a lot of sections are written alternating the impersonal form to the first-person plural. In particular, I found the discussion and conclusion too shorts and not supported by the references and by the discussion of the results obtained
A more detailed results about the dose difference of brainstem and spinal cord were added, and the additional discussion about brainstem and spinal cord and the discussion of larynx were also included. The results showed the regenerated plans guided by the predicted EUDs had better consistency and better dose sparing comparing to the manual plans, which could not been obviously seen in our previous using dose-volume model. The results showed the advantage of using biologically related model in knowledge-based planning. The conclusion has been revised.

Furthermore, there are some inconsistencies in the model used (number of epochs, number of train patients) that which leads me to the consideration that the work needs a more thorough and detailed review.
I recommend the authors to re-write the manuscript in a more proper and extensive manner, adding more details on the evaluation of the goodness of the model. Furthermore the dose difference to some organ (laryinx) is not negligible and should be discussed in more detail by the authors.
The methods and materials section had been re-written to make it more clear and more easily followed. The whole article had also been detailed modified and reviewed by the American Journal Experts. The result of larynx had also been discussed in more detail.

Minor comments
Page 4 (you should delete "the unless otherwise noted, the abbreviation DVH in this paper refers to a cumulative dose-volume histogram"
Has been revised.

Please spell DTH and OVH in the text
The definition of DTH and OVH has been added.

Line 24-29 Too long period, I suggest rephrasing
The methods and materials section had been re-written.

Line 48 showed THAT this method
Has been revised.

Page 5 Line 1-2 The present period is not clear, I recommend rephrasing it as in the abstract
Has been revised.

Page 5 Line 15-16: Please rephrase the period "The treatments were applied in recent 2 years. For the prescribed doses of all the plans in 30 or 31 fractions"
Has been re-written.

Page 5 line 17-22 I suggest to split the period in question, indicating the delineation modality for the three target and the corresponding margin used to move from GTV to PTV and to separate this part to the part with the dose to the three targets.
This part has been re-written and highlighted in the revised version.

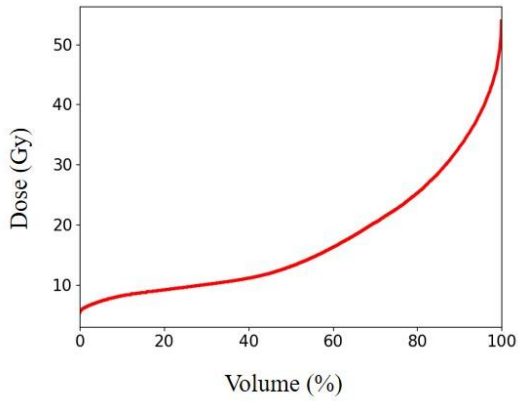
Page 5 Line 27-28 too colloquial period
Has been re-written.

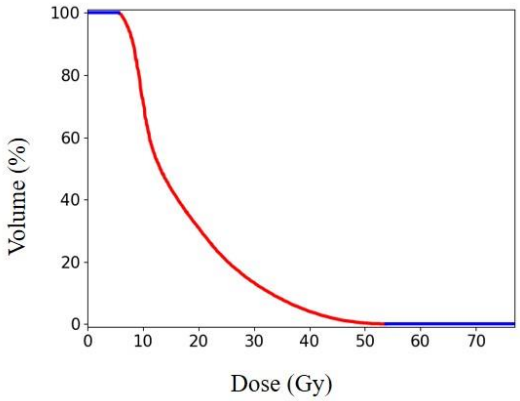
Page 5 Line 29 Period absolutely not clear. Please rephrase In addition to the clinical plans, a one-field PTV54-conformed radiotherapy plan was generated with the goal of 70 Gy to D98 were delivered PTV70 by the TPS for each patient
This part has been re-written and highlighted in the revised version.

Page 5 line 35 I would change the term adjusting in moving
Has been revised.

Page 5 line 46 brainstem and not brain stem
Has been revised.

Page 5 line 58 It's not clear for me to see the volume bin in percentage and not in absolute values. Please explain why you did this choice and in case what do you consider as percentage volume





The picture shows the different DVH forms adopted in this work and the previous work. We found that the contributions of MSE in equation (1) majorly came from the effective region (red line) in DVH. Percentage dose bin (0.1% in practice), rather than by absolute volume or dose values, helped focusing the neural network training attention on the effective region, which was shown to be helpful in improving the prediction accuracy through practical experiments. Besides, making the effective part of equal length could also help balanced the weights of different OARs in training process. The explanation had been included in the discussion section.

Page 6 line 7 means the volume proportion with deposition not greater than D is v. Please rephrase it

Has been revised.

Page 6 line 20 Overfitting and not overtraining

Has been revised.

Page 6 line 21-22 Period not clear

Has been revised.

Page 6 line 45 Please include detail of Monaco, such as Elekta, Sweden,…

Has been added.

Page 6 What is the batch size? At the beginning of the page, the authors state that 20 batches are used (line 5). At line 13 of the same page the authors state that 40 batches are used

In this study we carried out the training process with mini-batch strategy, a fixed number of training samples were randomly selected to train the model parameters every time, this fixed number was generally denoted as batch-size. In this study, the batch-size was set to 28 OAR DVHs (20 in the previous version was a mistake) divided the whole 1120 OAR DVHs from 80 training patients into 40 batches (14 OARs per patient included the brain stem, spinal cord, optic chiasm, optic nerves, lens, parotid glands, larynx, temporal lobes and the planning organ-at-risk volumes.). In practical, we found the training result not sensitive to the batch-size setting and we removed it in the revised version.

Page 6 line 49 patients and not patient
Has been revised.

How many patients do you use as testing cases? In the abstract you state 20 cases, in the manuscript 24…
20 testing patients, 24 was a mistake and had been corrected.

Page 7 line 16 please clarify what do you mean to inadequate optimization
α was set slightly smaller than 1 to achieve stricter constraints, we have re-written it and make it clearer.

Page 8 The results are not well presented in my opinion. The authors should show in separate manner the part related to the model elaborated and those related to the plan comparison.
Has been revised.

Page 8 Line 39-55 please include references.
Has been included.

Figure 1 - I recommend to include an image showing the whole workflow used to improve the clarity of the manuscript
Has been included.

Figure 4 - the y axis should be the same to make clearer the variability from different organs
Has been revised.

Reviewer #2: In this study the authors investigate a neural network approach to define optimal constraints for the optimization of VMAT treatment plans and apply the method to the dosimetric challanging case of nasopharyngeal carcinoma patients with simultaneous integrated boost.
A similar approach was recently published by the same group (DOI: 10.1088/1361-6560/ab5433).
In this work the authors use the equivalent uniform dose to train the model and focus on the region of the OAR not overlapping the PTV. Consistenlty with the findings of their own previous study, the neural network could be successfully trained.
Moreover, the plans which were re-optimized by using the starting constraints extimated by the trained neural network resulted in a PTV coverage equal to the original plans, but a better sparing of several organ at risk.

Interestingly, the sparing of the OAR seems to follow a different trade-off pattern

with respect to the their previous study, the major benefit being experienced by the brain stem and spinal cord, which were not highlightened in their previous work.

The dosimetric results were further improved compared to our previous work, which may be mainly owe to the EUD-based objectives allowing exploration of a much larger universe of solutions, making it easier for the optimization system to balance competing requirements in search of a better solution [14]. Besides, α in equation (5) also had certain affect, which was found in the trial and error process.

This part has been added to discussion section and highlighted.

The reviewer suggest that the authors briefly comment on that in the discussion, since the hence reported argument of overlapping PTV-OAR does not apply to those serial organs at risk.

This part has been added to discussion section and highlighted.

The results in Table 1 show the comparison of the maximum dose for brain stem and spinal cord. It would be intersting to see the comparison also for the dose received by a small volume (e.g. 0.1 cc or 1 cc, depending on the resolution of the dose calculation matrix).

The results for the dose received by 1 cc volume had been added to table 1 and showed remarkable differences.

The paper is generally well written and reads fluently. As minor remarks, the authors could consider defining in more details which clinical criteria were followed for the delineation of PTV60 and PTV54. In the introduction the acronyms DTH and OVH first appaers without definition.

This part had been rewritten with more details and the definition of DTH and OVH had also been added.
