

Title page

Study on the effect of DCGS on planned dose with 3DVH- γ analysis and bio-mathematical model for cervical cancer

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Abstract

Objective: The 3DVH- γ analysis and bio-mathematical model were used to analyze the effect of the dose calculation grid size (DCGS) on the planned dose (PD) for cervical cancer to explore the efficacy and sensitivity of the two methods in detecting dose changes.

Methods: 17 patients' plans for cervical cancer were enrolled (Pinnacle TPS, VMAT), and the DCGS was changed from 2.0mm to 5.0mm to calculate the planned dose respectively. The dose distribution calculated by DCGS = 2.0mm as the "reference" data set (RDS), the dose distribution calculated by the rest DCGS as the "measurement" data set (MDS), the 3DVH- γ passing rates and the (N)TCPs of the all structures under different DCGS were obtained, and then analyze the influences of DCGS on the γ passing rate and (N)TCPs and the relationship between their changes.

Results: The effect of DCGS on planned dose was obvious. When the γ -standard was 1.0mm, 1.0% and 10.0%, the difference of the results of the DCGS on dose effect could be detected by 3DVH- γ analysis ($p < 0.05$). With the decline of the standard, 3DVH- γ analysis' ability to detect this difference was also declining. When the standard was 1.0mm, 3.0% and 10.0%, the p value of > 0.05 accounted for the majority. With DCGS=2.0mm being RDS, $\Delta\gamma$ -passing-rate presented the same trend with Δ (N)TCPs of all structures except for the femurs only when the 1.0mm, 1.0% and 10.0% standards were adopted for the 3DVH- γ analysis.

Conclusions: The 3DVH- γ analysis and bio-mathematical model can be used to analyze the effect of DCGS on the planned dose, and the former's detection ability has a lot to do with the designed standard, and the latter's capability is related to the parameters and calculated accuracy of the latter.

Key words: 3DVH- γ analysis; bio-mathematical model; dose calculation grid size (DCGS); dose change

Introduction

The dose calculation grid size (DCGS) was a basic parameter setting in the design of the plan. Usually a commercial treatment planning system (TPS) will provide various DCGS within a certain range for designers to choose for different needs. For example, the commercial Pinnacle TPS provides DCGS ranging from 1.0mm to 10.0mm, and the default DCGS is 4.0mm. Larger DCGS is commonly adopted for calculation in cases with larger target volumes and organ-at-risk (OAR) volumes for better calculation efficiency. However, a smaller DCGS should be chosen for dose calculation in radiotherapy for head and neck tumor to obtain precise doses of small-volume OARs including lens, optic nerve and pituitary, etc., especially these OARs' maximum dose being important[1,2].

The difference in doses caused by different grid sizes may affect our evaluation of the quality of physical solutions, although the DCGS can not cause the actual absorbed dose when the accelerator's parameters are certain. (This is why the planned dose values and (N)TCP values calculated under different DCGS are all called "calculated" values in the following sections). Therefore, it is a crucial task to understand the effect of DCGS on the physical and biological doses in radiotherapy for cervical cancer (CC). γ analysis is currently the most common and generally accepted method for quantitatively assessing the difference between the two dose-distributions (DDs)[3,4]. It detects the difference between the two DDs by a designed γ standard (e.g. 3.0mm, 3.0%, 10%) and it will provide a report on passing rate. In intensity modulated radiation therapy (IMRT), γ analysis is usually used to analyze the difference between the TPS-outputted and the actual measured dose distribution to evaluate the degree of dose deviation caused by various reasons during the execution of the plan, and to determine whether a plan is to execute based on the evaluation. However, previous studies have shown that different dose QA systems have different ability to detect errors based on the dose distribution output by TPS. Hussein et al.[5] enrolled pelvis and head & neck IMRT and RapidArc™ plans, and compared the differences in the detecting dose error of five commercial products: PTW Verisoft, Delta4 software, SNC Patient, Varian Portal Dosimetry and IBA OmniPro. The results showed that for the same pass-rate criteria, different devices and software combinations exhibited varying levels of agreement with the predicted γ analysis. On the other hand, different gamma analysis standards will get different passing rates. Research by Heilemann et al.[6] showed that the 3.0mm, 3.0%, and 10.0% standards were not sufficient to detect the deviation caused by the MLC position uncertainty, and this standard, at least, has to be 2.0mm, 2.0%, 10.0%.

The focus on the variation of planned dose (PD) is due to the fact that it will cause changes in the biological effects. Specifically, in the clinical practice of radiotherapy, the alteration in physical dose will bring about changes in TCP and NTCP. Therefore, the current project, under the condition of DCGS changes, used the dose distribution calculated by DCGS=2.0mm as the reference data set (RDS) to explore the efficacy and sensitivity of the 3DVH- γ analysis and the bio-mathematical model on dose change detection by analyzing the 3DVH- γ passing rates of all structures and the relationship between γ passing rate and (N)TCP.

1. Materials and methods

1.1 Patient materials

A retrospective study was performed on the physical plan of 17 patients with CC who were treated in the Department of Radiation Therapy of our hospital from December 2017 to November 2018. And the 17 patients' plans were initially designed and evaluated with DCGS=4.0mm. The patient's PGTV volume was 20.0-395.0 cm³, and the PTV volume was 880.0-2587.0 cm³. The average volumes of the two target volume were 141.6 cm³, 1850.7 cm³, respectively. The targets' volume and OARs' volume are shown in [Table 1](#). The patient was in a supine position with both hands surrounding his head, and the patient was fixed with a thermoplastic mesh. The Siemens Somatom Sensation Open 24 CT (Siemens Co., Munich, Germany) was used as the data acquisition system. The range of scanning was from the head of diaphragm to lower 1.0cm of the bottom pubic symphysis. And the CT data of each patient was reconstructed with a 3.0 mm layer thickness, was transmitted to Pinnacle TPS 9.10.

1.2 Design of VMAT radiotherapy plan

17 patients were treated with a Versa HD linear accelerator (Elekta Medical Systems Co., Stockholm, Sweden) of 6 MV photon beams. The volumetric modulated arc therapy (VMAT) plan of a 360° full bow with 2 arcs was designed for every patient based on Smart Arc inverse optimization. The cost functions were shown in [Table 2](#). The doses were calculated with the CCC algorithm. Planning prescription setting was as follows: the planning target volume (PTV) prescription being 45.0-50.0Gy / 25F, and the planning gross tumor volume(PGTV) prescription being 60.0-62.5Gy / 25F.

All VMAT physical schemes were designed with Pinnacle TPS (version 9.10). When the default value was DCGS = 4.0mm, the planners optimized and adjusted the treatment plans for CC patients based on their own previous experience. After all the indicators of the plans met the clinical requirements, changed the DCGS (from 2.0mm to 5.0mm) and recalculated dose in the target volumes and OARs.

1.3 3DVH- γ standard and passing rate

After the emergence of IMRT technology, verification of radiation dose before the implementation of treatment has become a very important part of the radiotherapy process. Dose verification can be divided into point dosimetry verification, plane dosimetry verification and gel dosimetry verification. The point dosimetry verification and Gel dosimetry verification[7,8] have not been widely accepted because of various reasons, and the plane dosimetry verification has become a popular method. The commercially available PTW-ARRAYs[9] and IAB-ARRAYs[10] were the most popular tools for plane dose verification in the past. Using these ARRAYs masked many uncertainties in the actual execution, such as the uncertainty of gantry angle. So, Delta 4, ArcCheck and Octavius 4D were produced and gradually replaced these ARRAYs.

Although the tools advanced, there has been no fundamental change in analytical methods. The γ analysis has been used throughout IMRT dose verification. The commonly recommended γ analysis standards are 3.0mm, 3.0%, and 10% threshold [11,12], but studies have shown that, depending on the technology and the disease, we should adopt stricter standards or other supplement analysis to analyze errors[13,14]. This article was to investigate errors among planned dose caused by DCGS with dose distribution calculated by DCGS=2.0mm as RDS and the dose distribution calculated

by DCGS=3.0mm, 4.0mm, 5.0mm as MDS, respectively. And we thought the location uncertainty was scarcely influential element under the situation. Therefore, when setting the γ analysis standard, we setted the following 3 standards: 1.0mm, 1.0%, 10% threshold; 1.0mm, 2.0%, 10% threshold; 1.0mm, 3.0% , 10% threshold.

1.4 TCP and NTCP calculation

Some biologically related models for plan optimization and/or evaluation have been introduced into treatment planning tools for clinical use. A variety of dose response models with a series of organ-specific model parameters were reported in the literatures, and were widely accepted as follows[15,16]:

$$TCP = \frac{1}{1 + \left(\frac{TCD_{50}}{EUD}\right)^{4\gamma_{50}}} \quad (1)$$

$$NTCP = 1/\sqrt{2\pi} \int_{-\infty}^u e^{-t^2/2} dt \quad (2.1)$$

$$u = (EUD - TD_{50})/(mTD_{50}) \quad (2.2)$$

$$TD_{50}(v) = TD_{50}(1) * v^{-n} \quad (2.3)$$

$$EUD = (\sum_i v_i D_i^a)^{1/a} \quad (2.4)$$

Where, a is a organ-specific constant, and its corresponding value is in the literatures [17, 18]. v_i is the fractional volume of the organ receiving D_i . m and n are unique organ-specific constants[17, 18]. TD_{50} is an uniform dose that is obsorbed dose at a 50% complication probability, and TCD_{50} is an uniform dose that is obsorbed dose at a 50% control probability.

1.5 Statistical analysis

Origin 8.0 was used for drawing and SPSS 20.0 was used for statistical analysis.

2. Results

2.1 (N)TCP changes with DCGS

The 68 differential DVHs of 17 patients' radiotherapy plans (17*4=68) were exported as .txt data files. The data in the .txt file were read by MATLAB program and put into formulas (1) and (2.4) to calculate the EUD of each OAR and each target. Then TCP and NTCP were calculated using the formulas (1) and (2.1). Figures drawn by Origin 8.0 software were shown in Fig1. and Fig2. As shown in the figures, the influence of DCGS on the calculated value of (N) TCP was obvious, and the calculated value of (N) TCP decreased with the increase of DCGS.

Fig 1. Display of TCP change casused by DCGS

Fig 2. Display of NTCP change casused by DCGS

2.2 p-value analysis

The change of DCGS would bring about the change of each structure's absorption dose. In order to quantify the DC, we selected γ analysis to analyze difference between the dose corresponding to DCGS=2.0mm acting as RDS and the dose corresponding to DCGS=3.0mm, 4.0mm, 5.0mm acting as MDS, respectively.

In order to reflect the statistical significance of the dose difference caused by

different DCGS, we grouped and named the results of γ analysis, as shown in Table 3. For example, when the γ analysis standard setting was 1.0mm, 1.0%, 10.0% and the dose distributions of DCGS=3.0mm and DCGS=2.0mm were compared, the results were grouped as Aa. And the paired t test results of each structure were shown in Fig. 3. The γ -standard had a significant impact on the γ -analysis' sensitivity. When the γ -standard was 1.0mm, 1.0% and 10.0%, the difference of the results of the DCGS on dose effect could be detected by 3DVH- γ analysis ($p < 0.05$). With the decline of the standard, 3DVH- γ analysis' ability to detect this difference was also declining. When the standard was 1.0mm, 3.0% and 10.0%, the p value of > 0.05 accounted for the majority. It was a high probability event that the dose difference between DCGS=0.5mm and DCGS=3.0mm (or the other two DCGSs) could not be detected by this analysis.

Fig 3. The map of every structure's paired t test under varied γ analysis standard.

2.3 Correlation of Δ (N)TCP and $\Delta \gamma$

The (N)TCPs' and γ values both changed with DCGS. To explore whether there was a certain correlation between these two changes, we investigated Δ (N)TCP and $\Delta \gamma$ separately. Δ (N)TCP was defined as the (N)TCP value when DCGS=2.0mm minus the (N)TCP value when DCGS was other value. $\Delta \gamma$ was defined as 100.0% minus the γ passing rate when the dose of DCGS=3.0mm, or 4.0mm, or 5.0mm compared that of DCGS=2.0mm. Because γ analysis were carried out with three different standards in this paper, the $\Delta \gamma$ were divided into $\Delta \gamma_1$, $\Delta \gamma_2$ and $\Delta \gamma_3$ corresponding to 1.0mm, 1.0%, 10.0%; 1.0mm, 2.0%, 10.0% and 1.0mm, 3.0%, 10.0%.

In order to simplify the following writing, we describe the corresponding relationship as follows.

“M” corresponding to Δ (N)TCP = (N) TCP(DCGS=2.0mm) - (N) TCP(DCGS=3.0mm) and $\Delta \gamma = 100.0\% - \gamma$ passing rate when DCGS=3.0mm compared DCGS=2.0mm.

“N” corresponding to Δ (N)TCP = (N) TCP(DCGS=2.0mm) - (N) TCP(DCGS=4.0mm) and $\Delta \gamma = 100.0\% - \gamma$ passing rate when DCGS=4.0mm compared DCGS=2.0mm.

“L” corresponding to Δ (N)TCP = (N) TCP(DCGS=2.0mm) - (N) TCP(DCGS=5.0mm) and $\Delta \gamma = 100.0\% - \gamma$ passing rate when DCGS=5.0mm compared DCGS=2.0mm.

The Δ (N)TCP and $\Delta \gamma$ were shown in Table 4, Table 5 and Table 6. As shown in the tables, when the calculated values of (N)TCP of the targets, the bladder and the rectum decreased with DCGS increasing, the γ passing rate also decreased when the standard was 1.0mm, 1.0%, 10.0%.

3. Discussion and Conclusion

Compared with conformal radiotherapy, intensity-modulated radiotherapy can improve the conformal degree of the target area, reduce the dose of organs at risk, and reduce the acute and late toxicity of organs[19,20]. VMAT is a higher form of modulated radiation therapy, VMAT and IMRT have been compared in many studies[21,22]. The publications relating to planning[23], commissioning[24], QA[25] and clinical implementation[26] have been published, which made VMAT technology spread quickly around the world. Gantry rotation speed and dose rate vary when a VMAT schedule is executed, which made the complexity of VMAT QA be more than that of IMRT[27]. As

the origins of QA failure could be uneasy to confirm this failure caused by dose calculation from TPS, or dose delivery from linac, or detectors of phatom, or other aspects. Therefore, the source of the (N)TCP and γ passing rate was fixed on one factor DCGS.

It is an important basis for us to set up DCGS in the planning design to consider the efficiency of calculation under the precise of satisfying the accuracy of dose calculation. Many studies on SBRT have shown that, for SBRT, DCGS=2.0mm can meet the clinical requirements[28,29]. This conclusion was the main reason why in this paper we chose DCGS=2.0mm as the research basis. Secondly, the low computational efficiency of DCGS=1.0mm makes it difficult in clinical practice, when was DCGS=1.0mm, the Pinnacle TPS would spend about two 2.0 hours to calculate once a dose distribution for a patient.

Gamma analysis is a commonly used method to compare differences between two dose distributions, but the ability of gamma analysis to detect errors is closely related to the criteria set. Fig. 3 of the “**p-value analysis**” in this paper showed that when 1.0mm, 1.0% and 10.0% was used as the standard in the γ analysis, there was a statistical difference ($p < 0.05$) between any two results of γ analysis when DGCS was 3.0mm, 4.0mm or 5.0mm vs 2.0mm, indicating that the Gamma analysis was sensitive to changes of DCGS. However, when 1.0mm, 3.0% and 10.0% was used as the standard in γ analysis, there was mostly no significant difference ($p > 0.05$) between any two results of γ analysis when DGCS was 3.0mm, 4.0mm or 5.0mm vs 2.0mm, and at this time the Gamma analysis was not sensitive to changes of DCGS. Many studies’ results all reflected the similar conclusion of γ -standard and γ analysis’ sensitivity[30,31]. The difference was that these studies had set change of the standard in two dimensions (distance and dose) at the same time, for example, change the $\gamma_{3.0\%, 3.0\text{mm}}$ to $\gamma_{2.0\%, 2.0\text{mm}}$. When the dose standard of γ analysis was relaxed from 1.0% to 3.0%, the “dose points” of 1.0% < dose error < 3.0% that failed with the standard of 1.0mm, 1.0% and 10.0% were allowed to pass, so the ability of γ analysis to detect dose error ϵ [1.0%, 3.0%] was lossing. At the same time, we could also get from the results that the majority of the dose "calculated value" changes as DCGS from 2.0mm to 5.0mm were < 3.0%.

However, the situation was different when the (N)TCP biological mathematical model was used to detect these dose changes, and theoretically any DS caused by DCGS could be represented in the value of (N) TCP as long as the value of (N) TCP was accurate enough. So, when we changed DCGS we got the trend of (N) TCP and Δ (N) TCP, even though Δ (N) TCP was not a big value. In the study, Δ NTCP of the Femurs was always 0.00 in Table 6. It was not because NTCP did not change, but because the value was omitted because of too small, which was cause by parameters’ value of NTCP model.

The TCP and NTCP were expected to be obtained by studying the targets’ and OARs’ physical dose, because the two formers were of greater clinical significance. So this paper studied the relationship between Δ (N)TCP and $\Delta\gamma$. With the DCGS becoming larger, the relatively-lower-dose in the normal tissues located around the target was more calculated into the target, so the overall dose of the target decreased

and the TCP decreased. The focused irradiation mode of radiotherapy determines the general trend of dose decrease from the target area to the periphery, with the highest dose in the target. In this paper, we investigated the OARs, bladder, rectum, and femurs were the organs of adjacent to the targets, as the DCGS became larger, their relatively-high-dose was "deprived" by the targets, and the dose "deprived" by them from their surrounding was relatively-high-dose, so the DCGS became larger, their overall doses were falling, and their NTCPs were falling.

The 3DVH- γ analysis and bio-mathematical model can be used to analyze the effect of DCGS on the planned dose, and the former's detection ability has a lot to do with the designed standard, and the latter's capability is related to the parameters and calculated accuracy of the latter.

Abbreviations

DCGS	dose calculation grid size;
PD	planned dose
DVH	dose-volume histogram;
RDS	reference data set
MDS	measurement data set
TCP	tumor control probability
NTCP	normal tissue complication probability
TPS	treatment planning system
OAR	organ-at-risk
CC	cervical cancer
DD	dose distribution
IMRT	intensity modulated radiation therapy
VMRT	volumetric modulated arc therapy
PTV	planning target volume
PGTV	planning gross tumor volume

Declarations

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Authors' contributions

HB conducted all digital analyses and performed the statistical analysis. HB and XRW made substantial contributions to the conception and design of the work. HB, SJZ and XHL were major contributors in drafting and writing the manuscript. FHC, JWY, SJZ were responsible for radiation treatment planning. The author(s) read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to the General Data Protection Regulation (GDPR) but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

The authors agreed to publish this paper in Radiation Oncology

Competing interests

The authors declare that they have no competing interests.

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