A clinically relevant online patient QA solution with daily CT scans and EPID-based in vivo dosimetry: a feasibility study on rectal cancer

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Abstract

Objective. Adaptive radiation therapy (ART) could protect organs at risk (OARs) while maintain high dose coverage to targets. However, there is still a lack of efficient online patient quality assurance (QA) methods, which is an obstacle to large-scale adoption of ART. We aim to develop a clinically relevant online patient QA solution for ART using daily CT scans and EPID-based in vivo dosimetry. Approach. Ten patients with rectal cancer at our center were included. Patients’ daily CT scans and portal images were collected to generate reconstructed 3D dose distributions. Contours of targets and OARs were recontoured on these daily CT scans by a clinician or an auto-segmentation algorithm, then dose-volume indices were calculated, and the percent deviation of these indices to their original plans were determined. This deviation was regarded as the metric for clinically relevant patient QA. The tolerance level was obtained using a 95% confidence interval of the QA metric distribution. These deviations could be further divided into anatomically relevant or delivery relevant indicators for error source analysis. Finally, our QA solution was validated on an additional six clinical patients. Main results. In rectal cancer, the 95% confidence intervals of the QA metric for PTV $D_{95}$ (%) were $[−3.11\%, 2.35\%]$, and for PTV $D_{2}$ (%) were $[−0.78\%, 3.23\%]$. In validation, 68% for PTV $D_{95}$ (%) and 79% for PTV $D_{2}$ (%) of the 28 fractions are within tolerances of the QA metrics. One patient’s dosimetric impact of anatomical variations during treatment were observed through the source of error analysis. Significance. The online patient QA solution using daily CT scans and EPID-based in vivo dosimetry is clinically feasible. Source of error analysis has the potential for distinguishing sources of error and guiding ART for future treatments.

1. Introduction

Adaptive radiation therapy (ART), which was proposed by Yan et al (1997), utilizes various feedback, such as daily images, to rapidly modify a radiotherapy plan during the whole treatment course. However, due to technical and resource limitations, the large-scale clinical practice of ART is still lacking. At technical level, there are three main obstacles in ART: the lack of high-quality image acquisition, rapid treatment planning and online plan quality assurance (QA) solutions. With the emergence of MR-Linac (Mutic and Dempsey 2014), CT-Linac (Yu et al 2021) and artificial intelligence (AI) technology (Sun et al 2022), there may be solutions to the first two
obstacles (Brock et al 2017, Corradini et al 2019). For online plan QA, more research is needed to find an appropriate solution (Glide-Hurst et al 2021).

Many studies have used deep learning based or deformable registration based methods to generate synthetic CT because cone beam CT (CBCT) only or MR images only could not be used directly for dose calculation (Giacometti et al 2020, Chen et al 2021, Zhao et al 2021). These methods may introduce additional uncertainty in dosimetry (Thummerer et al 2020, Xu et al 2021). Strict alignment of voxel information between CBCT and planning CT need to be guaranteed but it is difficult to achieve in practice (Sun et al 2021) and inaccurate HUs or image artifacts are still exist in synthetic CT (Dai et al 2021). 4% deviation in some dose-volume indices or 5% decrease in gamma passing rate (GPR) can be observed, and this degree of deviation could not be accepted in QA procedure (Veiga et al 2014, Giacometti et al 2019, Dai et al 2021). Researches about in vivo dosimetry based on EPID and CBCT also reported a similar way of synthesize CT for dose calculation (Ali et al 2013, Rozendaal et al 2015, Lim et al 2019, Olaciregui-Ruiz et al 2020). The evaluation metrics in these in vivo dosimetry studies were GPR, dose-volume index, dose at one point or volumetric changes. And there is no consensus about the tolerance thresholds.

Many issues about online patient QA remain unresolved. First, patient QA metrics are weakly related to the dose deviation that is clinically relevant (Stasi et al 2012). Commonly used metrics, such as the GPR (Piron et al 2018, Gray et al 2021), cannot reflect the dose deviation on critical organs at risk (OARs) (Nelms et al 2013). Second, there is no consensus how to set an appropriate tolerance for different tumor sites (Stanhope et al 2015, Miftan et al 2018, Piron et al 2018, Lambrecht et al 2019). Third, especially for ART, the cause of the dose deviation may not be easily distinguished (Bossuyt et al 2020, Olaciregui-Ruiz et al 2021). Deviation in the measured values may result from variation in a patient’s anatomy or inaccuracy in the delivery devices (Piron et al 2018).

Aiming to resolve these issues, we propose a clinically relevant online patient QA solution for ART. With diagnostic low-dose daily CT scans on which dose distribution can be directly calculated and EPID-based in vivo dosimetry, the dose distribution that a patient received can be reconstructed as accurately as possible. By comparing this reconstructed dose distribution to the planning dose distribution, a clinically relevant QA tolerance is established. Meanwhile, sources of error are investigated by comprehensively analyzing various types of metrics.

The solution directly connects to the dose-volume indices that physicians and physicists are concerned about, and a tolerance setting method based on the treatment history was proposed. Moreover, source of error analysis could help physicists with follow-up actions. To demonstrate the proposed solution, the implementation and validation results of data from patients with rectal cancer are presented as an example in this study.

We briefly describe the device and related algorithm used in section 2.1. Then, the proposed QA solution is introduced in section 2.2. The implementation and validation results of data from patients with rectal cancer are demonstrated in section 2.3., while the detailed results are presented in the results section.

2. Materials and methods

2.1. Device and algorithm

All treatments were delivered on a uRT-Linac 506c medical linear accelerator (United Imaging Healthcare, Shanghai, China), which has a diagnostic-quality 16-slice helical CT imager coaxially attached to the gantry of a C-arm linac and is equipped with an amorphous silicon EPID XRD1642 (Varex Imaging, UT, USA). The EPID imager could acquire portal images of 40.96 × 40.96 cm² size at the detector plane. Additional details of the device description can be found in our previous studies (Feng et al 2021, Yu et al 2021).

The Monte Carlo-based dose reconstruction algorithm was provided by and integrated into UIH TPS (United Imaging Healthcare, Shanghai, China). This algorithm only uses EPID data and patient daily CT scans to calculate the reconstructed dose distribution. A series of algorithm verifications was performed before this study, and the details and results are presented in the supplement.

2.2. Proposed online QA solution

Figure 1 shows a general workflow to establish the QA protocol and criteria for a specific tumor site. Inspired by the concept of confidence intervals in statistics, a similar idea was used to determine the tolerance of dose deviations. Therefore, a group of patients with the same tumor site were required to establish the dose deviation distribution.

These patients were treated with routine radiotherapy procedures, and two types of data were collected during treatment, including pretreatment low-dose daily CT scans, which were used to perform image-guided radiation therapy (IGRT), and transmission portal images at every angle for each fraction. These data were used
to calculate a series of dose-volume indices and perform the following analyses: (1) QA metrics calculation; (2) tolerance settings; and (3) source of error analysis.

2.2.1. QA metric calculation
To estimate the actual dose that patients received in a single fraction, the dose distribution is calculated by a dose reconstruction algorithm on daily CT scans with EPID data, and the dose-volume indices need to be calculated on recontoured region of interests (ROIs). The PTV of daily CT scans may need to be manually delineated by the same physician following the same guideline as during initial contouring, while OARs can be delineated by an automatic segmentation algorithm if consistent with the treatment planning process.

The abbreviation DRR represents the dose-volume indices obtained from daily CT scans with recontoured ROIs and EPID-based reconstructed dose distribution. Compared to dose-volume indices from other combinations, the deviations between these specific indices and the original treatment planning indices are closest to the true deviations between treatment delivery and planning. Therefore, the percentage of this deviation was used as the QA metric of the dose-volume index.

2.2.2. Tolerance and action level setting
A critical issue for patient QA is the tolerance setting. Inspired by the concept of confidence intervals, a statistics-based tolerance level was proposed based on a series of dose-volume indices. These indices were selected based on clinical considerations, such as the $D_{95}$ ($D_n$ in Gy means dose corresponding to $n\%$ volume) of the PTV.
Before dose-volume index calculations, physicians and physicists were required to review the daily CT scans and reconstructed dose distributions to ensure that there were no outliers in the sample data for the tolerance level setting. The 95% intervals are regarded as the tolerance range. The Shapiro-Wilk (SW) test was used to decide whether each index followed a normal distribution. A normal distribution was fitted if it was followed, and 95% interval was decided by $[\mu - 2\sigma, \mu + 2\sigma]$, where $\mu$ is the mean value of the metric and $\sigma$ is the standard deviation; otherwise, the ranges from the 2.5% to 97.5% quantiles were used as the 95% interval.

2.2.3. Sources of error analysis
The dose-volume deviation can be divided into anatomically relevant and delivery relevant deviations. By further analyzing the data of QA metric, the source of the error may be located. For a certain dose-volume index, the deviation between daily CT scans and planning CT scans with the same dose type (both are forward calculated or reconstructed) can be used to indicate the impact of anatomical variation, while deviation between reconstructed dose and forward calculated dose in the same CT scans can be used to indicate the impact of delivery errors. For example, (equation (1)), the deviation between DRR (daily CT scan with recontoured ROIs and reconstructed dose distribution) PTV $D_{95}$ and planning (PPF, dose-volume indices obtained using planning CT scans with planning ROIs and forward calculated dose distribution) PTV $D_{95}$ can be divided into two deviations: the deviation between DRR PTV $D_{95}$ and DRF (daily CT scan with recontoured ROIs and forward calculated dose distribution) PTV $D_{95}$ and the deviation between DRF PTV $D_{95}$ and planning PTV $D_{95}$. The former represents the delivery deviation, and the latter represents the impact of anatomical variation

$$\frac{\text{DRR PTV } D_{95} - \text{PPF PTV } D_{95}}{\text{PPF PTV } D_{95}} = \frac{\text{DRR PTV } D_{95} - \text{DRF PTV } D_{95}}{\text{PPF PTV } D_{95}} + \frac{\text{DRF PTV } D_{95} - \text{PPF PTV } D_{95}}{\text{PPF PTV } D_{95}}$$

(1)

### 2.3. Implementation and validation of rectal cancer
#### 2.3.1. Patients and data
The treatments of ten patients with rectal cancer at our institution from March 2021 to July 2021, were analyzed to establish the tolerance level. In total, 45 daily CT scans were taken of these patients. All patients were treated with 6 MV photon intensity-modulation radiation therapy (IMRT) or volume-modulation arc therapy (VMAT) with a prescribed dose of 50 Gy/25 fractions or 25 Gy/5 fractions. The ROI contouring was mainly based on RTOG 0822 (Hong et al 2015). The detailed information of plan settings was listed in table 1, and the optimization constraints in table 2. All optimization goals followed this template and oncologists modified the specific dose value for each goal based on prescription and their personal experiences. A point dosimetric verification on phantom before the first treatment has been performed for each patient.

#### 2.3.2. Dose-volume indices selection
Based on our clinical routine, 10 indices of the ROIs were selected in this study, namely $D_{95}$, $D_{2}$, homogeneity index (HI) and conformity index (CI) of the PTV (defined in equations (2) and (3)); $D_{15}$ and $D_{50}$ of the bladder; and $D_{25}$ and $D_{40}$ of the left or right femoral head (FH-L or FH-R). To demonstrate the clinical use of these indices, we set 4 QA metrics out of tolerance as action levels. For the patient who have more than 4 indices out of tolerance, a review by physicist will be required.
Table 3. Errors deliberately introduced to original plans.

| Error type | Gantry angle (°) | Collimator angle (°) | MLC shift (mm) | MU scaling (%) |
|------------|------------------|----------------------|----------------|----------------|
| Magnitude  | −3, −5, 3, 5     | −3, −5, 3, 5         | −3, −5, 3, 5   | 3, 5           |

Note: MLC shift means both leaf banks of all leaves shift in the same direction.

\[
HI = (D_2 - D_{98}) / D_{Rx} \tag{2}
\]

\[
CI = (V_{Rx,PTV})^2 / (V_{PTV} \times V_{Rx}) \tag{3}
\]

Note: \(D_{Rx}\) means prescription dose, \(V_{Rx,PTV}\) means the volume with dose larger than prescription dose in PTV, \(V_{PTV}\) means the volume of PTV, and \(V_{Rx}\) means the volume with dose larger than prescription dose in the body contour.

2.3.3. Source of error analysis

Similar to PTV \(D_{95}\) in equation (1), total deviations of other indices for rectal cancer used in this study are decomposed into delivery relevant deviation and anatomically relevant deviation. The decomposition pattern is represented in equation (4), in which \(I\) represent the indices of PTV \(D_{95}\), PTV \(D_{2}\), Bladder \(D_{15}\), Bladder \(D_{50}\), FH-L \(D_{25}\), FH-L \(D_{45}\), FH-R \(D_{25}\) and FH-R \(D_{40}\).

\[
\frac{DRR I - PPF I}{PPF I} = \frac{DRR I - DRF I}{PPF I} + \frac{DRF I - PPF I}{PPF I} \tag{4}
\]

Note: DRR, dose-volume indices obtained using daily CT scans with recontoured ROIs and reconstructed dose distribution; DRF, dose-volume indices obtained using daily CT scans with recontoured ROIs and forward calculated dose distribution; PPF, dose-volume indices obtained using planning CT scans with planning ROIs and forward calculated dose distribution; and \(I\), the dose-volume indices for rectal cancer.

Common anatomical variations were included in the clinical data of the 10 patients, while delivery errors were relatively small and not easy to distinguish. To demonstrate the effectiveness of the source of the error analysis, a few delivery errors were deliberately introduced into the original plan of the 10 patients. The plans with delivery error were forward calculated and regarded as reference plan, and the original plans with portal images were used to reconstructed dose distribution. The error types and error magnitudes are shown in table 3. Small errors within the tolerance of TG142 (Klein et al 2009) were not considered, and errors with too large a magnitude were almost impossible in the clinic and also not included.

2.3.4. Solution validation

An additional 6 rectal cancer patients with a total of 28 daily CT scans from April 2021 to November 2021 were analyzed to validate our proposed solution. These patients were treated with 6 MV photon IMRT or VMAT with a prescribed dose of 50 Gy/25 fractions, and their PTVs on daily CT scans were also recontoured by the same clinician so that the QA metric of them could also be evaluated.

3. Result

3.1. QA metric and tolerance

The distribution and the tolerance of the ten QA metrics are shown in figure 2. All SW test results and specific values of tolerance ranges are shown in table 4. Four indices had SW \(p\)-values smaller than 0.05. For PTV \(\Delta D_2\), Bladder \(\Delta D_{15}\) and Bladder \(\Delta D_{50}\), the top point on the curve is close to the median, while other occurrences are approximately symmetrically distributed around the median, creating a downward-sloping curve on each side of the peak. These trends suggest a possibility of normal distribution with more data. For PTV \(\Delta HI\), since HI usually increases as the plan quality declines, most values of PTV \(\Delta HI\) is positive and the curve is a unilateral descent, thus, it may not be normally distributed in nature.

3.2. Source of error analysis

Based on the data from one patient, the total deviation, anatomically relevant deviation and delivery relevant deviation during the whole treatment (5 fractions) are shown in figure 3. In this patient’s data, the main error relates to anatomical deviations. This deviation occurred mainly in the bladder, which means that this organ shows anatomical variation between treatments.

The tolerance calculated in section 3.1 was used to evaluate these error-relevant deviations. Table 5 shows the number of dose-volume indices that are out of tolerance with or without delivery error introduced. For
nonerror-introduced fractions, all delivery relevant deviation indices are within tolerance. There were no fractions with four or more out-of-tolerance indices about the three types of errors.

3.3. Solution validation

The distribution of the QA metric dose-volume indices for the data from 6 additional patients is shown in figure 4. The 96% fractions for Bladder $\Delta D_{50}$ (\%), the 100% fractions for FH-L $\Delta D_{25}$ (\%) and the 96% fractions for FH-L $\Delta D_{40}$ (\%) are within tolerance. However, only 54% of the fractions for PTV $\Delta CI$ (\%) are within tolerance.

Table 6 shows the number of dose-volume indices that are out of tolerance for 28 validation fractions. There were 5 fractions with four or more out-of-tolerance metrics in total deviation. After review of a physician, these 5 fractions are considered clinically acceptable.

3.4. An example of solution application

By examining the data, we found that one patient’s data had a fraction with 5 QA metric dose-volume indices out of tolerance, including PTV $\Delta D_{95}$ (\%), PTV $\Delta D_{2}$ (\%), Bladder $\Delta D_{15}$ (\%), FH-R $\Delta D_{25}$ (\%), and FH-R $\Delta D_{40}$ (\%).

For source of error analysis, this fraction had 3 anatomically relevant indicators out of tolerance, Bladder $\Delta D_{15}$ (\%), FH-R $\Delta D_{25}$ (\%), FH-R $\Delta D_{40}$ (\%), and 1 delivery-relevant indicator out of tolerance, PTV $\Delta D_{2}$ (\%).

The planning ROIs and daily recontoured ROIs of the fraction for the patient are shown in figure 5. A shift of the right femoral head and an extension of the PTV can be observed. Our solution can quantitatively identify the dosimetric impact of these anatomical variations. The DVHs of the planning and QA metric indices are shown in figure 6. A decrease in the dose of PTV and an increase in the dose of the FH-R can be observed.
4. Discussion

There are three major innovations in this study. First, the solution can directly connect to the dose volume indices that physicians and physicists are concerned about, and the impact on each ROI can be quantified.

Second, by using 95% intervals, we proposed a setting method for the tolerance range based on a cohort of patients treated at the same body region. Third, by calculating anatomically relevant and delivery relevant indices, more information could be provided to physicists for follow-up actions.
In this study, 45 fractions of 10 patients were enrolled for the tolerance setup, and 28 fractions of 6 patients were enrolled for validation, this is because recontouring ROIs is a time-consuming and labor-intensive task for physicians. For clinical use in future, more data and a more sophisticated workflow may be required for data processing.

Since the MR-Linac was introduced for clinical use, an increasing number of studies investigated how to perform online QA for ART plans (Winkel et al. 2019). Wang et al. (2017) and Nachbar et al. (2021) proposed a method to calculate dose distribution based on pretreatment MR images. However, without PTV recontouring and EPID dose reconstruction, this forward calculated dose distribution may still differ from the dose distribution patient received. For example, we forward calculated PTV \( D_{95} \) using daily CT scans with transferred ROIs after rigid registration based on Monte Carlo algorithm, the Pearson correlation coefficient between this type of PTV \( \Delta D_{95} \) (%) and the QA metric for the 45 patients is moderate \( (\rho = 0.573) \).

By using EPID reconstructed 3D dose distribution, Olaciregui-Ruiz et al. (Torres-Xirau et al. 2020, Olaciregui-Ruiz et al. 2021). proposed an automatic dosimetric verification method that can be implemented on MR-Linac. Two comparisons were performed, including gamma analysis (3%/2 mm/10% threshold) and comparison of the median dose to the high-dose volume (HDV \( \Delta D_{50} \)). 85% for the gamma pass rate and 5% for HDV \( \Delta D_{50} \) were used as tolerance limit values. These two indices may not relate to the indices that are of concern to the physician. Further sensitivity studies are necessary for the optimal determination of indicators and tolerance limit values (Torres-Xirau et al. 2020, Olaciregui-Ruiz et al. 2021). Some EPID-based method for ART using in aqua portal dosimetry with dose inhomogeneity conversion maps or portal images only, and 3D GPR (2 mm/2%, 50% threshold) of 0.70 could be achieved (Matsushita et al. 2020, Olaciregui-Ruiz et al. 2022). These methods may have the drawback of inability to accurately estimate the dose delivered to the patients.

In error source analysis, for nonerror-introduced fractions, all delivery-relevant indices were within tolerance, and the distribution of the anatomically relevant indices was similar to the distribution of total deviation (table 5). For error introduced fractions, the distribution of the anatomically relevant indices was

![Figure 4. Distributions of the QA metric metrics of 28 validation fractions. Red vertical lines indicate the 95% confidence intervals determined in section 3.1.](image)

| Number of out-of-tolerance indices for one fraction [indices] | Anatomical + delivery [fractions] | Anatomical [fractions] | Delivery [fractions] |
|-------------------------------------------------------------|----------------------------------|-----------------------|---------------------|
| All indices within tolerance                                | 12 (42.9%)                       | 13 (46.4%)            | 22 (78.6%)          |
| 1 index out of tolerance                                    | 6 (21.4%)                        | 7 (25.0%)             | 6 (21.4%)           |
| 2 indices out of tolerance                                  | 4 (14.3%)                        | 4 (14.3%)             | 0 (0%)              |
| 3 indices out of tolerance                                  | 1 (3.6%)                         | 4 (14.3%)             | 0 (0%)              |
| 4 indices out of tolerance                                  | 4 (14.3%)                        | 0 (0%)                | 0 (0%)              |
| 5 indices out of tolerance                                  | 1 (3.6%)                         | 0 (0%)                | 0 (0%)              |
| Total                                                       | 28 (100%)                        | 28 (100%)             | 28 (100%)           |
similar to the nonerror-introduced fractions (table 5). However, the number of delivery relevant indices appeared. For the fractions with more than 4 out-of-tolerance indices, the distribution of delivery relevant indices was similar to the distribution of the total deviation. This indicated that our solution has some potential for distinguishing error sources.
During solution validation, the values of two indices \([\text{PTV}\Delta CI\text{%}]\) and \([\text{FH-R}\Delta D40\text{%}]\) had relatively low proportions within the tolerance. After reviewing the data, we found that two patients had all fractions out of tolerance in these two indices (the patient whose data is shown in figures 5 and 6 is one of them). These two patients may have a deviation in setup between planning and treatment.

Our method relies on the acquisition of portal images and CT scans, as well as the reconstruction algorithm of 3D dose, thus their uncertainty may affect the results. This study verifies that the system can detect a certain degree of setup error and delivery error through phantom validation, which is presented in the Supplement. Further researches may be required to quantify the impact of these uncertainties.

This study has some limitations. First, in the tolerance setting, 95% interval and 4 out-of-tolerance QA metrics were partly subjective. The main reason is that there is not enough data. As we mentioned above, recontouring ROIs is a time-consuming and labor-intensive task for physicians. With accumulating more data, these setting can be improved. Second, anatomical variances from daily CT scanning to treatment delivery or during treatment delivery, such as the movement of the patient after position setting, and the movement of the patient’s internal organs, were not distinguished in this study.

Our proposed method is an ART QA solution. Because the indices used in this solution were clinically relevant dose-volume indices, this solution can also be used for ART patient monitoring, especially for anatomically relevant indices. Further data and research are required in this direction.

5. Conclusion

The aim of this article was to develop a clinically relevant online patient QA solution, and the online patient QA solution proposed using daily CT scans and EPID-based \textit{in vivo} dosimetry is clinically feasible. Tolerance and action level setting using distribution of dose-volume index is comparatively reasonable. Source of error analysis has the potential for distinguishing sources of error and guiding ART for future treatments. Further studies and more data are required to improve the efficiency and model accuracy for clinical use.

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Ethical statement

This retrospective study was reviewed and approved by the Institutional Review Board of Fudan University Shanghai Cancer Center (2201250-16) and the requirement for individual informed consent was waived.

Conflicts of interest

YL is employed by United Imaging Healthcare Corporation.

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