Radiotherapy delivery error detection with electronic portal imaging device (EPID)-based *in vivo* dosimetry

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To the Editor: Due to the highly complex nature of intensity-modulated radiotherapy (IMRT) planning and delivery, patient specific quality assurance (PSQA) should be implemented to assure the reliability of treatment delivery and improve the treatment efficacy. A pre-treatment PSQA program is a routine procedure in IMRT and, to some extent, can avoid serious errors in dose delivery. However, there is no guarantee that the dose delivered to the patient is the same as planned, due to the patient's anatomical change, setup uncertainty, and organ motion during treatments. Therefore, *in vivo* dosimetry (IVD) has been recommended as part of routine IMRT to monitor the actual dose delivered to the patient, detect the source of errors, and assist in adaptive therapy.

Currently, the electronic portal imaging device (EPID) has attracted much attention as a tool of IVD because of its fast image acquisition, high resolution, simple setup, and digital format. The commonly used EPID is the solid detector amorphous silicon (a-Si) system. When EPID performs image acquisition, the fluorescence generated by the scintillation phosphor layer is converted into the electron-hole pair of a photo-diode matrix. The transistor voltage is changed to output a digital image when enough signals are collected. EPID has a series of dosimetric characteristics such as buildup effect, optical glare, ghosting effects, etc., which should be considered to ensure the accuracy of EPID dosimetry. EPID dosimetry applies forward- and back-projection methods to perform IVD. For forward-projection, EPID transit images are predicted using Monte Carlo simulation or other analytical methods, and then compared with measured images. The predicted transit images can also be converted into 2D transit dose images. For back-projection, measured EPID

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images are back-projected to the patient computed tomography (CT) images, combined with the dose deposition kernel, to obtain a 2D or 3D dose distribution of patients.

EPID-IVD showed the potential for error detection in some studies. Mans et al^[1] developed an offline EPID-IVD system using the back-projection method at the Netherlands Cancer Institute. Seventeen serious errors were detected among 4337 verified treatment plans collected between January 2005 and August 2009. Subsequently, they have completely replaced the pre-treatment PSQA procedure with this system. After that, some studies have investigated EPID-IVD for detecting potential errors caused by unintended variations, such as machine- or patientrelated errors. Currently, there are three main methods to simulate the errors: (1) modeling potential errors by introducing modifications to the treatment plan, (2) obtaining experimental samples by measuring the phantom dose distribution, and (3) using modified CT images to introduce errors. A summary of the published studies that have investigated the detectability of errors using offline EPID-IVD systems is presented in Supplementary Table 1 [http://links.lww.com/CM9/B510]. There are also some commercial offline EPID-IVD systems released, including SunCHECK (Sun Nuclear, Melbourne, FL, USA), Adaptivo (Standard Imaging, Middleton, WI, USA), Edose (Raydose, Guangzhou, China), EPIgray (DOSIsoft, Cachan, France), SOFTDISO (Best Medical Italy, Chianciano, Italy), iViewDose (Elekta, Stockholm, Sweden), Dosimetry Check (MathResolutions, LLC., Columbia, MD, USA), and others.

With the development of stereotactic body radiotherapy (SBRT), a high dose can be delivered in a few fractions, online EPID-IVD systems are urgently needed. In

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2015, an online EPID-IVD system was developed by Woodruff et al.^[2] The EPID time-resolved images were predicted using a forward-projection method and compared with the EPID images taken during treatment. The system will create an alert if over four consecutive frames with a gamma pass rate below 40% are found. The simulated catastrophic errors can be detected within 0.1 s. The Netherlands Cancer Institute developed an online EPID-IVD system for real-time treatment verification in 2016. Unlike Woodruff's system, they used a back-projection method to reconstruct 3D dose distribution in real-time, rather than EPID images. To achieve "real-time", dose reconstruction speed was accelerated to be faster than the EPID frame rate. This system can halt the linear accelerators (LINAC) immediately for serious delivery errors. Recently, an intelligent EPID-IVD system, built in an integrated CT-LINAC (uRT-LINAC 506c, United Image Healthcare, Shanghai, China), has been developed. This system can enable offline 3D patient dose reconstructions, and also perform online EPID image comparison and raise an alert when the errors are out of tolerance. Some other online EPID-IVD systems were also investigated using forward- or back-projection methods for detecting machine and patient-related errors. A summary of the published studies using online EPID-IVD systems for error detection is shown in Supplementary Table 1 [http: //links.lww.com/CM9/B510].

The performance of the EPID-IVD system, either offline or online, depends, to a large extent, on the detectability of the introduced errors. In general, both the online and offline EPID-IVD systems mentioned above have shown better detectability for multi-leaf collimator (MLC) leaf position shifts, monitor unit (MU) errors, and aperture size errors, but worse detectability for gantry angle errors and patient position shifts.

The detectability of the specific errors should be considered to improve the performance of the EPID-IVD system. The selection of alert criteria will affect the detectability of the errors. A small tolerance limit for the variations to the expected values may result in low specificity (false positive) and increase unnecessary extra inspection workload. Similarly, a large tolerance limit will result in low sensitivity (false negative), which may result in errors being missed. In addition, EPID image acquisition modes, time-resolved or time-integrated, can also affect the detectability of different error types. The detection of MLC leaf position errors can be improved dramatically with EPID time-resolved mode, while using time-integrated EPID mode, the errors occurring at certain control points may be averaged out when all control points in each arc in volumetric-modulated arc therapy (VMAT) are accumulated. The EPID with integrated mode for pre-treatment PSQA had the same limitation. The detection of anatomical errors can be improved with time-resolved EPID mode because more sources of information can be collected, such as contour projections of each control point, which is beneficial for the categorization of anatomical changes.

In addition to the detectability of errors, the response speed is also important for performance improvement, particularly for the online EPID-IVD system, which can interrupt the treatment immediately if significant errors are detected.

It is important to note that while the series of studies and commercial systems described above demonstrate the capability of EPID-IVD for error detection, the system cannot directly tell what these error sources are. Therefore, a method that can quickly detect and classify the error source is highly desirable and needed. This enables timely adjustment of treatment plan or re-acquisition of images and re-positioning, toward adaptive radiotherapy. In recent years, more and more studies have applied machine learning (ML) and deep learning (DL) models in radiotherapy. But only a few studies focused on detecting the errors occurring during treatment.

Liu *et al*^[3] introduced position uncertainties in left-right (LR), anterior-posterior (AP), and superior-inferior (SI) directions in the delivery of Graves' ophthalmopathy radiotherapy plans to a head phantom during treatment, and used ML model and convolutional neural network (CNN) model to classify patient position errors. They also developed a deep neural network model with structural similarity difference and orientation-based loss to classify these errors to improve the classification performance. Only the patient's position uncertainties were simulated, the anatomical errors were not considered in their studies.

Wolfs et al^[4] proposed a CNN model to identify anatomical errors, position errors, and mechanical errors, which were simulated by modifying CT images and treatment plans. Three error magnitudes were used to categorize the errors. Wolfs *et al*^[4] showed that the DL model with EPID dosimetry can identify the types and magnitude of errors during delivery and achieve automatic error classification and detection in an in vivo scenario for the first time. But only time-integrated EPID images were used in their study, and errors per beam segment could not be detected. Bedford and Hanson^[5] used a recurrent neural network (RNN) model, which can learn the measured images at each segment from a temporal series of inputs, for rapid error detection in real time. They introduced machine-related errors and patient-related errors to train the RNN model. Results showed that the RNN model can improve the timeliness of error detection by about 30%. Although ML/DL models have shown the potential for error detection and classification in IMRT PSQA, there are still some issues worth further investigation before routine clinical application.

First, it is difficult to obtain anatomical error data from actual treatment to set the "ground truth" to train and test ML/DL models. Therefore, the proposed ML/DL models in existing studies are based entirely on simulations, which have limited applicability to the real situation. In addition, the simulation study ignored the uncertainties in the actual treatment process and the EPID dosimetry process, which may affect the ability to detect clinically relevant deviations. To overcome this problem, the model training and optimization process should be based on the clinical data to ensure that the actual uncertainties are incorporated into the model.

Second, the error classification system based on ML/DL models can only identify those errors in relation to which they have been trained. The above-mentioned studies focused on a single type of error, while multiple errors often interweave with each other in the real clinical environment. The more complex scenarios in which multiple errors occur simultaneously should also be examined in future studies.

Finally, the EPID-IVD system could be used in conjunction with some image-guided radiotherapy devices (CBCT/ CT-based systems, MRI-LINAC, etc.), which can account for ongoing changes in the patient's anatomy during the treatment. Recently, Chen et al^[6] developed an error classification method with uRT-LINAC 506c (United Image Healthcare, Shanghai, China). They used patient daily CT to recontour regions of interest (ROIs), and combined daily CT with portal images to reconstruct 3D patient dose distributions, after which dose-volume indices were computed based on recontoured ROIs and planning ROIs. The deviation of dose-volume indices between recontoured ROIs with planning ROIs was used to indicate anatomical errors, and the deviation between reconstructed dose distributions with forward calculated dose distributions in the same daily CT was used to indicate delivery errors.

Overall, EPID-based IVD systems have shown good error detectability during treatment, but these systems cannot directly ascertain what these errors are or distinguish them. Recently, it has been shown that ML/DL models can directly detect and distinguish errors that may occur during treatment, but there are still some issues that need to be addressed before the routine clinical application.

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