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Future directions of in vivo dosimetry for external beam radiotherapy and brachytherapy

1. Introduction

Radiation therapy is a highly complex process involving teams from different disciplines. Prompted by this complexity and subsequent potential risk of treatment errors, radiation oncology has been a pioneer in the implementation of incident learning systems and prospective risk management in medicine. These efforts have made radiotherapy a safe medical discipline. However, despite the low risk of severe incidents, several registries have documented errors happening in radiotherapy. These errors range from near-misses to severe over and under dosages (for a recent overview, see [1]) and include also an unknown number of undetected errors, the false negatives.

For external beam radiotherapy (EBRT) many radiotherapy institutes participate in dosimetry audits to verify independently their local practice. One study from the Imaging and Radiation Oncology Core Houston Quality Assurance Center (IROC-H) recently reported [2] the results of an IMRT dosimetry audit for a head&neck phantom with thermoluminescent detectors (TLD) and film gamma analysis. They showed that 10% of participating institutes with a wide range of operational size failed to meet criteria of better than ±7% dose agreement with TLD or ≥85% of pixels satisfying a (7%, 4 mm) dose difference/distance to agreement criterion with film. One could assume that it is mostly complex plans that fail, but conflicting reports exist on this in the literature [3,4]. There may be some evidence that plans consisting of many small field segments may lead to larger uncertainties [5]. The IROC study mentioned may be an extreme case, since especially in Europe usually higher compliance rates are reported (see [6] and references therein). The large reported differences in compliance rates may reflect differences in codes of practice, complexity of the audits, postal or onsite audits, detectors used etc. Although highly recommended, audits can also not guarantee treatment quality on other days. Furthermore, for brachytherapy (BT) less auditing and less verification, in particular during therapy, is performed than for EBRT.

The emphasis of verifying the radiotherapy treatment chain is currently mainly on equipment and dosimetry checks which are performed pre-treatment. However, these checks cannot catch a variety of errors occurring during delivery of the actual treatment e.g. related to patient geometry or to applicators for brachytherapy. Therefore, a substantial need exists for systems that can constantly monitor deviations in the treatment dose that may be relevant to the outcome of the treatment. The most direct way to assess the treatment dose is through in vivo dosimetry (IVD). After the first ESTRO Physics Workshop, held in Glasgow in November 2017, it was decided to start a Task Group on IVD, with the aim of providing reports on the use of IVD for both EBRT and BT. This editorial gives an overview of the requirements identified by the Task Group, while more details for the individual modalities can be found in the respective reports published in this and the previous volume [7,8].

2. Scope

The EBRT and High Dose Rate (HDR) BT reports [7,8] followed a unified IVD approach. Much attention was given to electronic portal imaging detector (EPID) panels for EBRT and on time resolved dosimetry for brachytherapy. The purpose of the reports was to identify the key reasons for low adoption of IVD in the clinic and to specify the requirements needed for advancing the field to a significantly higher adoption in clinical practice.

The current Task Group did not focus on Low Dose Rate BT and EBRT methods such as electron beams, Tomotherapy, CyberKnife, Halcyon, kilovolt photon beams, ion beams and MR-linac.

3. Definition

Before embarking on this mission, it was important to formulate a general consensus definition of IVD, which was then used in the two ensuing reports (for BT and EBRT).

IVD is a radiation measurement that is acquired while the patient is being treated, containing information related to the absorbed dose in the patient. This definition implies that an IVD system must be able to capture errors due to equipment failure, errors in dose calculation, patient/applicator positioning errors, and patient anatomy changes.

In this definition, “Patient positioning error” refers to EBRT and “applicator positioning error” to BT.

More details on which methods are included and excluded from this definition and further specific refinements for IVD for EBRT and BT are given in the two reports [7,8]. These also state which developments are needed to turn some methods into true IVD.

4. Aims

An IVD method should satisfy at least one, but preferably all four, of the following aims:

1. To provide a safety system to catch planning or treatment errors that can significantly affect the patient
2. To provide tools for treatment adaptation, i.e. to correct a fractionated therapy, either during the treatment or before the next fraction
3. To record the true dose received by the patient compared to the planned dose

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4. Be practicable and comfortable for the patient.

Ideally, an IVD system should record a signal in real time that can be converted to a dose without perturbing the patient dose itself. The 'real time' aspect is important to catch (gross) treatment errors before they can affect the patient e.g. in hypofractionated EBRT or BT. Modern information analysis methods such as artificial intelligence based systems to detect errors and their possible causes may also play a role in the further development of IVD.

5. Requirements

The conclusions of the EBRT and BT IVD reports can be summarized by a number of requirements. IVD is an ideal technique to check independently that all radiotherapy fractions, and all parts of it are correctly administered. However, the full benefit of any approach is only reached if the techniques: 1) are commercially available, 2) are straightforward to implement in clinical practice, 3) require minimal and easy to perform QA procedures, 4) are accurate enough to detect relevant errors with acceptable false positive and false negative rates, 5) have acceptable requirements for resources and manpower, 6) are preferably fully automated, and 7) are fully integrated in the patient workflow.

For current IVD systems, there are in general issues with one or more of these requirements. This has so far impacted the clinical adoption of IVD leading to a general under-utilisation. IVD is currently facing problems both on the sides of clinics and device manufacturers of commercial technology: many clinics do not perform IVD because the clinical benefit is considered too low or because the workflows for usage and/or QA are too demanding with regard to complexity and need for resources. Secondly, although there are quite a few manufacturers in the field, their willingness to invest in IVD is affected by the limited demand from clinics as well as the lack of recommendations and regulations. Thirdly, there is a lack of clinical guidance on the tolerance and action levels, and on how to perform sensitivity and specificity assessments. However, new techniques for IVD are being continuously developed and when combined with automated analysis tools and potential automated treatment interrupt capabilities, IVD has significant potential to facilitate wide clinical use to benefit patient safety.

6. Need for further development

The Task Group identified the available technologies and raised awareness to both users and manufacturers for further required developments in both hardware and software. In general, more research is needed to explore fully the capabilities and limitations of IVD methods for various treatment modalities. The following aspects were identified for further development:

- The sensitivity and specificity of IVD systems, to ensure that systems can identify clinically relevant errors while balancing the amount of false alarms
- The workload and resources needed for clinical implementation, maintenance, QA and daily operation
- The (automatic) data processing and the comparison between predicted and measured signal from IVD systems
- The degree of automation of the systems
- The possibility to derive optimal clinical decision criteria for customized error detection
- The technical specification of the system which is provided by IVD vendors to the users
- The integration of IVD systems with current non-IVD methods.

The authors hope that clinical users and device vendors may find inspiration in these reports to accelerate the clinical introduction of IVD methods.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Review Article

In vivo dosimetry in external beam photon radiotherapy: Requirements and future directions for research, development, and clinical practice☆

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ABSTRACT

External beam radiotherapy with photon beams is a highly accurate treatment modality, but requires extensive quality assurance programs to confirm that radiation therapy will be or was administered appropriately. In vivo dosimetry (IVD) is an essential element of modern radiation therapy because it provides the ability to catch treatment delivery errors, assist in treatment adaptation, and record the actual dose delivered to the patient. However, for various reasons, its clinical implementation has been slow and limited. The purpose of this report is to stimulate the wider use of IVD for external beam radiotherapy, and in particular of systems using electronic portal imaging devices (EPIDs). After documenting the current IVD methods, this report provides detailed software, hardware and system requirements for *in vivo* EPID dosimetry systems in order to help in bridging the current vendor-user gap. The report also outlines directions for further development and research. *In vivo* EPID dosimetry vendors, in collaboration with users across multiple institutions, are requested to improve the understanding and reduce the uncertainties of the system and to help in the determination of optimal action limits for error detection. Finally, the report recommends that automation of all aspects of IVD is needed to help facilitate clinical adoption, including automation of image acquisition, analysis, result interpretation, and reporting/documentation. With the guidance of this report, it is hoped that widespread clinical use of IVD will be significantly accelerated.

1. Introduction

External beam radiotherapy (EBRT) with photon beams has seen major progress in recent decades in the form of treatment planning, beam delivery, and image guidance. Nonetheless, despite best efforts, the actual delivered dose to the patient can differ from the planned dose. Among the many reasons for this are inaccuracies in the calculations of treatment planning systems (TPSs), errors in plan transfer to the accelerator or in beam delivery, and differences in patient geometry between the planning and treatment stages. The three aims of *in vivo* dosimetry (IVD) [1] are to catch treatment errors, assist in treatment adaptation, and record the actual dose delivered to the patient. Therefore, one would expect that IVD is already an essential link in the clinical workflow of modern radiotherapy. However, very few radiotherapy centers perform IVD during beam delivery [2]. The current standard is to perform dosimetry checks using pretreatment dose measurements in phantoms, which requires major resources but cannot catch errors related to patient geometry or in beam delivery during the actual treatment [3].

The purpose of this report is to analyze why IVD currently is not routinely performed, which methods are available, which methods need more development, and what needs to be done to augment clinical acceptance of the various methods. Although IVD is a widely applied term, its use easily causes misunderstandings not only between vendors

☆ During the 1st ESTRO Physics Workshop celebrated in November 2017 in Glasgow, Scotland, a task group was created to stimulate the wider adoption of in vivo dosimetry for external beam photon radiotherapy. The members of this task group, authors of this report, were selected on the basis of their expertise to contribute relevant input to the area of study and their long-term experience in the clinical implementation of in vivo dosimetry systems.

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and users but also within the research community. In order to prevent future misinterpretations, a concise definition of IVD in the scope of EBRT is provided in the Methods section. According to this definition, point detectors placed on the patient's skin in the treatment field such as thermoluminescent detectors, silicon diodes, metal-oxide semiconductor field-effect transistors, optically stimulated luminescence dosimeters, and electronic portal imaging devices (EPIDs) [4,5] are the main commercially available IVD methods. Due to the limitations of point detectors for large-scale implementation of IVD in modern EBRT, the emphasis of this report lies on EPID-based IVD (EIVD) systems. EPIDs are nowadays ubiquitous on modern accelerators, they are easy to use, they have potential for automation and they can perform dosimetric verification in 2D or 3D. The use of EPIDs for dosimetric measurements has matured for both pre-treatment patient-specific quality assurance (QA) [6] and IVD [7–10]. The various EPID dosimetry approaches have been discussed in a comprehensive way in a review article by van Elmpt et al. [11], and have been discussed further in the updated literature review by McCurdy et al. [12]. Currently, commercial EPID dosimetry software products are available from several vendors. While vendors generally provide specific guidelines and overall support for the implementation of their EIVD system, the user has an important role in commissioning and implementation of these systems. However, there are currently no specific guidelines for users of EIVD systems on the potential, limitations and correct utilization of EIVD systems.

This report identifies system, software, hardware and user requirements needed for the widespread clinical implementation of EIVD systems. While mainly directed at vendors, these requirements should be of help in bridging the current vendor-user gap. To ensure a clear understanding of these requirements, the main concepts and basic terminology for the current types of EIVD methods are introduced. Finally, further directions for development are proposed to vendors and researchers in areas where improvements are needed for a wider adoption of EIVD systems. The report focuses on the use of EIVD systems for common external photon beam technology. Other IVD systems are only briefly discussed.

2. Methods and materials

2.1. IVD definition

IVD is a radiation measurement that is acquired while the patient is being treated containing information related to the absorbed dose in the patient. This definition implies that an IVD system must be able to capture errors due to equipment failure, errors in dose calculation, patient positioning errors, and patient anatomy changes.

The definition excludes all 'transmission dosimetry' methods that capture only the accelerator exit dose/energy fluence (or related quantities or metrics) before the beam reaches the patient, even if these are combined with a cone beam computed tomography (CBCT) image acquired right before treatment delivery. Using an accelerator log file, even in combination with a CBCT image, is also not considered IVD. The aforementioned systems can, however, complement IVD methods. Also, the comparison of an EPID image made during a specific fraction of a patient treatment with a reference EPID image, e.g., of the first fraction, may miss dose errors present in the reference image and is therefore a constancy check but not *in vivo* dosimetry. While such methods can be valuable tools for patient-specific QA, they are currently not categorized as IVD.

2.2. Structure of task group report

While the emphasis of this report lies on EIVD systems, the report presents first a brief state-of-the-art overview of the use of point detectors where their future role and limitations are recognized. As was the case with the definition of IVD, and to avoid misinterpretations, this report covers the main concepts and defines a basic terminology for the current types of EIVD systems. This terminology is used to guide readers through the next sections.

The report identifies a list of system, software, hardware and user requirements needed for the widespread clinical implementation of EIVD systems. Requirements are presented for the overall EIVD system, as well as for the different subsystems: EPID imager, image acquisition software and EIVD software. Specific requirements for automation are also provided as they are key to guarantee an optimal balance between resources and performance. The requirements list was elaborated first by the members of the task group with experience implementing EIVD systems and then reviewed by the rest of the task group members following an iterative process. Further recommendations are made for vendors and researchers in areas where improvements are needed for a wider clinical adoption of EIVD systems.

The references in the manuscript were selected to assist in the narrative of the report either by providing evidence for particular statements or by pointing to extra sources for further technical details but are not needed to understand the text. The references were screened for their inclusion by all members of the task group first and later by the advisory group.

3. Current IVD methods

3.1. Point detectors

Many types of point dose detector systems are available for IVD. The most commonly used are diodes, thermoluminescent dosimeters, and metal-oxidesemiconductor field-effect transistors. Optically stimulated luminescent dosimeters and plastic scintillation detectors have recently come into use for IVD [13–19]. The use of detectors for IVD in EBRT requires calibration methods to correlate the detector reading with the delivered dose [20,21]. Point detectors, either placed on the skin of the patient or embedded in the immobilization mask or frame, are typically used to measure entrance dose and/or exit dose. In conformal beam radiotherapy, entrance IVD can detect major errors, mainly those caused by incorrect beam parameter settings (data transfer between planning and delivery) or machine malfunctions [22]. Before the widespread use of record-and-verify systems and the automatic transfer of all beam parameters from the TPS to the treatment units, entrance IVD was shown to detect data transfer errors [23]. By combining entrance with exit measurements, differences in patient anatomy between planning and delivery can also be detected [24]. However, the transition from simple conformal fields to intensity-modulated techniques such as intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) has limited the usefulness of point measurements [25,26], particularly when bearing in mind the additional uncertainty due to placement error, which can substantially impact measured-to-planned dose agreement of point detectors in high gradient regions, demonstrating the criticality of accurate dosimeter placement for IMRT and VMAT treatments [27].

Point detectors that can be placed inside a catheter or implanted near the tumor can provide direct verification of the actual dose delivered to the tumor or organ at risk [15,28,29]. The main limitation of these detectors for clinical implementation is their invasiveness. Even when placement of the detector near the tumor is possible, the location of the detector, combined with changes in patient anatomy, means that the results may have large uncertainties. In addition, the dose can be checked at only one or a few points. Finally, point detectors may perturb the dose.

Point detectors are useful in determining skin dose and peripheral dose (e.g., contralateral breast, lens of eye, scrotum), as most TPSs do not provide accurate dose calculations in these situations. Point detectors can also confirm that cardiovascular implantable electronic devices (e.g., pacemakers) receive a minimal dose (below the manufacturer's specified dose limits) [30]. In the absence of TPSs, such as for total body irradiation or intraoperative radiation therapy, IVD with

point detectors has proven to be valuable [31–34].

Even if point detectors still have a role for 3D conformal beam radiotherapy, for skin and peripheral dose measurements, for special techniques, and for dosimetry audits for clinical trials [35], their limitations of for large-scale implementation of IVD are obvious. First, point dosimetry is insufficient for patient-specific QA in modern EBRT. Point detectors are cumbersome and intrusive, add extra time to treatment delivery, cannot be automated and require well-trained staff. Due to the recognized limitations of point detectors for a widespread implementation of IVD, the focus of this report is on the use of EPID dosimetry for IVD.

3.2. EPID dosimetry for IVD

Although initially developed for patient setup verification, EPIDs show also useful dosimetric characteristics [36–39] that have made them suitable for the implementation of IVD verification solutions [8,40–50]. Beginning in the early 2000 s, the current generation of amorphous-silicon flat-panel EPID technology became commercially available from major linac manufacturers and today is a ubiquitous choice on newly purchased linacs. The primary layers of an amorphous silicon EPID detection structure are a buildup or interaction layer, which is usually copper; a scintillating phosphor layer, usually gadolinium oxysulfide; and the photo-diode matrix, whose support material is amorphous silicon. Owing to the high atomic number (Z) of the materials and the inherent beam-energy spectrum, the response of the EPID will differ from ion-chamber measurements. Other factors that modify the spectrum, such as patient attenuation, field size, off-axis distance, and patient-to-EPID distance, also contribute to this difference. All EIVD systems use the measured image signal from the transmission energy fluence that impinges on the detector. This is affected by: (1) the incident beam fluence from the linac impinging on the patient, (2) primary fluence attenuation in the patient, (3) scatter from the patient, and (4) the response of the EPID to (2) and (3).

Typically, EIVD assessments are performed by combining the data of all EPID frames acquired during delivery. *Time-resolved* analysis refers to assessments using subsets of frames or cumulative frame signals. These frames can be grouped according to time, control point, or gantry angle. *Offline* assessment is performed after delivery and can be performed using both time-resolved and non-time-resolved methods [7,44]. *Online* assessment is performed in real time using time-resolved analysis so that assessment is made before the total dose has been delivered to the patient, with the aim to interrupt treatment [51,52]. Supplementary Table S7 provides a brief overview of currently available EIVD systems. These systems do not all comply with all of the requirements formulated in this report.

3.2.1. Forward systems at the EPID level

A direct method of EIVD is to predict and compare the *measured portal image* signals to a *predicted portal image*. This method uses the treatment plan and planning CT with a physics model that typically includes an incident fluence model, a patient attenuation and scatter model, a treatment couch attenuation model, and an EPID energy deposition model. Monte Carlo and analytical techniques have been used in this approach [46,53-55]. Another closely related method is to predict the dose to a water slab at the position of the EPID, i.e., a *predicted portal dose image*. This method requires an algorithm to convert the measured signals to dose in water or *measured portal dose image* including corrections for energy-dependent response [56].

Most implementations to date employ *non-time-resolved* methods using the integrated image signal; however, for VMAT, this obviously has major limitations. Time-resolved analysis for VMAT deliveries can be performed following alignment of predicted and measured images [44,57]. Experience with an online system using comparison of predicted to measured portal images has been reported [51].

A disadvantage of these types of EIVD methods at the plane of the EPID is that the comparisons are not intuitive and cannot easily be related to clinically relevant comparison metrics such as patients' dose volume histograms. However, they do not contain any *less* information on the delivery than back-projection systems. Generally, 2D planar gamma analysis is employed, but other metrics have also been investigated [58].

3.2.2. Back-projection systems within the patient: dose reconstructed within a patient model

These systems estimate a point dose or dose distribution within a patient model from the measured EPID image. When the patient model is a CBCT scan acquired immediately prior to treatment, then the dose is an estimate of the *delivered* dose for that treatment fraction as it accounts for the anatomy of the patient before the delivery [45,59]. When, as is more common, the patient model is the planning CT scan, then the estimated dose in this model can be used to determine a *change* in the delivery from the planned delivery. A recent paper studied the effect of the choice of patient model on the performance of *in vivo* 3D EPID dosimetry [60]. In this paper, it was concluded that with planning CT images as patient model, EPID dose reconstructions underestimate the dosimetric effects caused by errors in patient positioning and overestimate the dosimetric effects caused by changes in patient anatomy.

For *direct back-projection* systems the primary fluence at the plane of the EPID is usually derived by correction of EPID scatter and patient scatter. This fluence is back-projected through the patient model and combined with dose-deposition kernels to determine the dose distribution [42,61]. Solutions have been presented to compensate the suboptimal support for density inhomogeneities in these simple dose calculations [62,63]. Other empirically based approaches have been developed to determine dose at a point or a plane in the patient model from the EPID image [64,65]. For *indirect back-projection* systems, the primary fluence is back-projected through the patient model to determine the incident fluence to the patient. This is then used with a conventional patient dose-calculation engine and analytical and Monte Carlo methods have been employed [47,66,67].

The clear advantages of back-projection systems are that the estimated dose is more intuitive and that differences can be evaluated by direct comparison to the planned dose distribution in the patient model using gamma or dose volume histogram evaluations. The majority of implementations have been offline, although an online system has also been reported [52]. For back-projection systems for VMAT, a time-resolved acquisition and back-projection method is required; however, the analysis is typically based on the integrated back-projected signal [43]. A brief overview of the currently available EIVD methods is presented in Table 1.

Table 1
Currently available types of EIVD systems.

System type	Comparison location	Prediction	Measured/EPID-reconstructed
Forward systems (EPID)	EPID plane	Predicted portal image. Grayscale values.	Measured portal image. Grayscale values.
Forward systems (dose)	EPID plane	Predicted portal dose to water slab.	Measured portal dose to water slab.
Back-projection systems (direct)	Within patient model	Treatment planning system. Dose in patient model.	Dose back-projection directly into patient model.
Back-projection systems (indirect)	Within patient model	Treatment planning system. Dose in patient model.	Dose back-projection through patient to incident fluence. Calculate dose in patient model.

4. Requirements for EPID-based IVD systems

Detailed software and hardware requirements regarding the overall system performance, as well as EPID imager, MV image acquisition software and IVD software are presented as Supplementary Material, see Tables S1–S4.

Furthermore, for a successful large-scale implementation, EIVD systems must ensure a manageable and configurable workload to guarantee an optimal balance between resources and performance [7,8,48,68]. Automation is essential for large-scale clinical implementation of EIVD systems because it reduces the number of labor-intensive, time-consuming, and error-prone tasks [69,70]. Automation also allows for more frequent use of the system, e.g., for all fractions. See Supplementary Table S5 for the specific list of requirements on the automation steps. In case automation is only partly available, the whole verification process must be carefully described, and an estimation of the workload required to perform the non-automated tasks must be provided. Note that full automation is a requisite for online assessments.

In an automated environment, the inspection of alerts becomes the only remaining work. Vendors are expected to facilitate a streamlined workspace for the timely inspection of alerts (Requirements S5.7 and S5.8) and additional tools to aid in the alert inspection work (S4.13–15). An estimate of the average per-treatment alert-management workload must also be given. Fig. 1 displays a flow chart illustrating the basics of an EIVD alert-inspection workflow.

The commissioning of the EIVD system also demands resources and manpower. Vendors are expected to provide information about the commissioning equipment and the measurement procedures, expected workload, acceptance tests and acceptance criteria [71–73]. Regarding periodic QA procedures, the test frequency, equipment, expected workload and automatic possibilities must also be known.

5. Future directions for research, development and clinical practice

5.1. Uncertainties

IVD systems need to assess whether the actual dose delivered to the patient D_D lies within agreed-upon dosimetric lower and higher tolerance limit values (T_L, T_H) with respect to the originally intended planned dose value D_P [74]. In this assessment, the measured *in vivo* dose value D_{IVD} is used for an estimation of D_D. The uncertainty U_{IVD} in the D_{IVD} measurement defines the range of values (and their probability) within which D_D is expected to lie. The probability density function of delivered dose values PDF_{DD} is used to calculate the likelihood that the delivered dose deviation will exceed the tolerance limit values (see Fig. 2) and needs to be taken into account when defining dosimetric action limits for IVD systems. Note that for EIVD, the meaning of 'dose' differs among systems, and 'value' is often not a point dose value but a 2D/3D dose distribution.

EIVD vendors, possibly in collaboration with users across multiple institutions utilizing different technologies, should put efforts into determining U_{IVD} for all dose comparison indicators and clinically relevant combinations of delivery techniques and treatment disease sites, see Requirement S1.13. The determination can be made by comparing D_{IVD} dose values against reference values that can be reasonably used as D_D or by simply considering the inherent spread of D_{IVD} dose values in

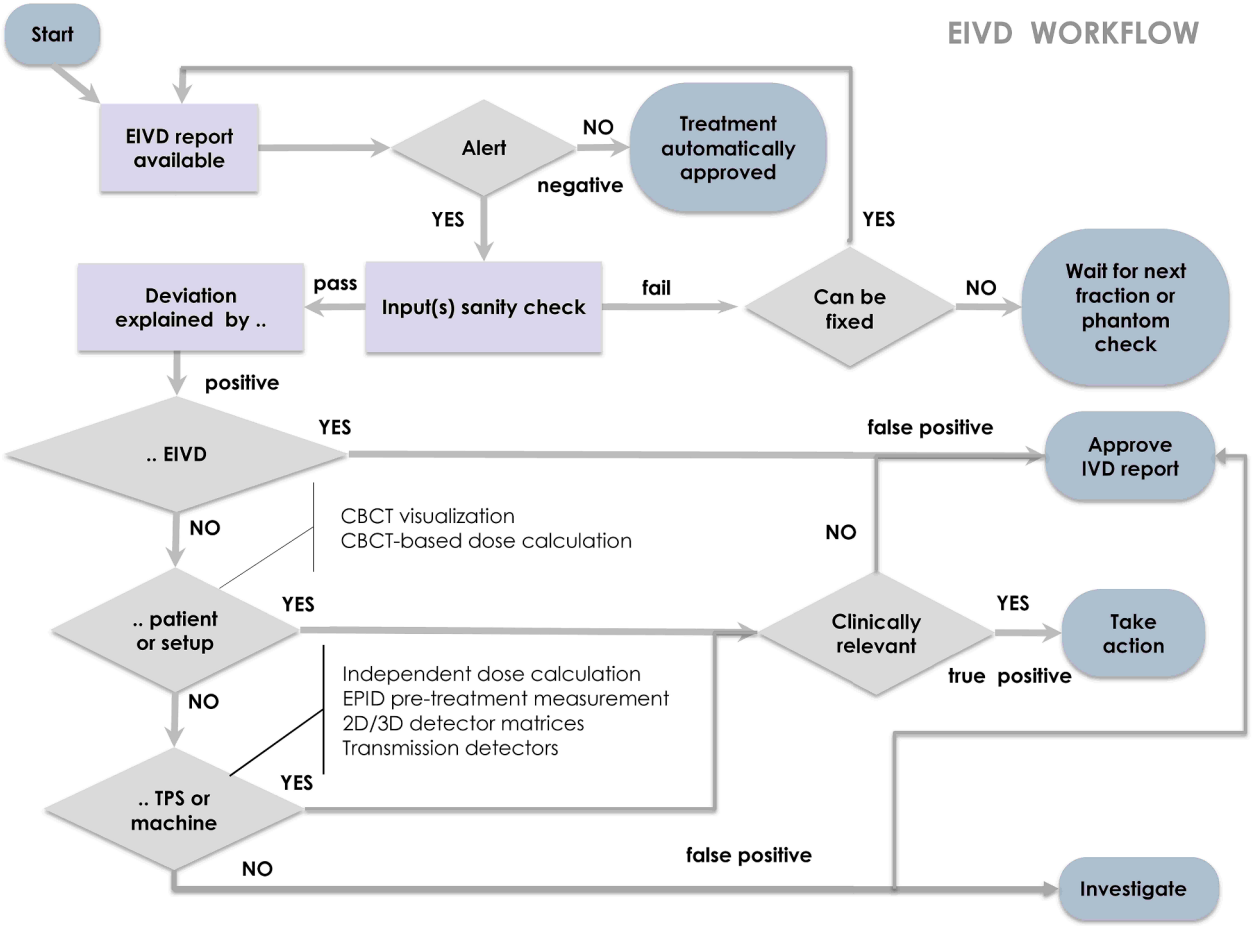

Fig. 1. Basics of an EIVD alert-inspection workflow.

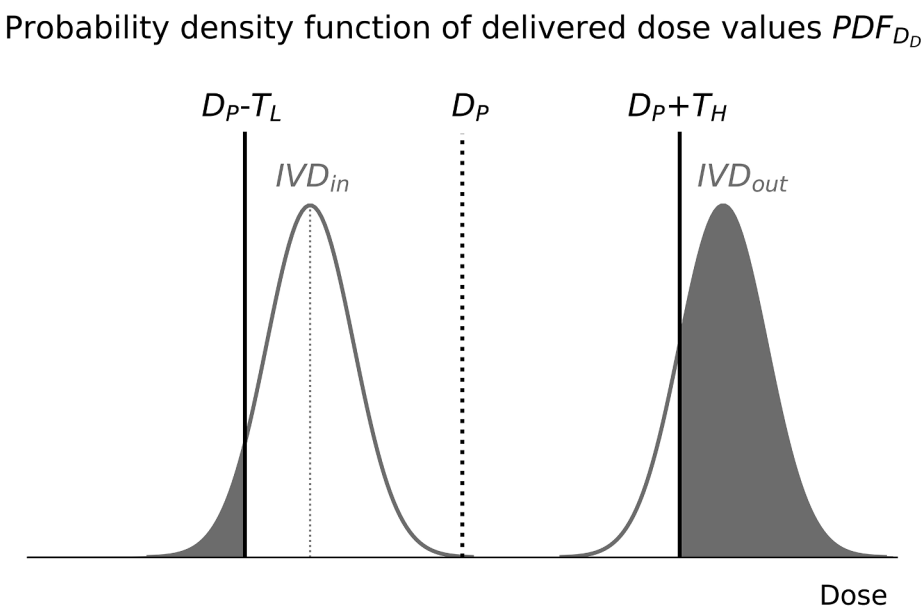

Fig. 2. Probability density functions of delivered dose values corresponding to two D_{IVD} measurements, one inside (IVD_{in}) and one outside (IVD_{out}) the dosimetric tolerance limit values ($D_P - T_L$, $D_P + T_H$). The graph illustrates how the uncertainty of the IVD system influences the likelihood that the actual delivered dose deviation will exceed the tolerance limits (gray shaded areas). For simplicity, U_{IVD} is assumed to follow a normal distribution without bias.

nominally "error-free" deliveries. It may be insightful to evaluate the uncertainty of the system for increasing levels of complexity: (i) simple plans, e.g. square fields, on homogeneous phantoms, (ii) complex plans on homogeneous phantoms and (iii) complex plans on anthropomorphic phantoms. In addition, extra uncertainties in case of uncorrected errors in patient positioning and/or anatomy changes if daily patient imaging is not used in the reconstruction should be evaluated.

The presence of a bias in U_{IVD} distributions would suggest that there is a systematic error in the determination of D_{IVD} dose values that needs to be corrected.

Furthermore, EIVD vendors need to explain the main causes for uncertainty and put efforts into not only assessing but also reducing the uncertainty.

5.2. Error detection

The ultimate goal of IVD is error detection, i.e., to detect deviations between planned dose distributions and delivered dose values exceeding specified tolerance limits. An overview with the errors that EIVD systems are expected to detect is presented as Supplementary Material, see Table S6. The detectability of a specific type of error depends very much on the specificity and sensitivity of a particular EIVD system for that type of error, as discussed in the next section. Mijnheer [75] presented an overview of the different types of errors detected by various groups using both in-house-developed and commercial EIVD systems. In this overview, examples of point-dose errors, errors in the 2D or 3D features of leaf sequencing, dose calculation errors, and patient-related errors are shown. Bojechko et al. [76] analyzed a series of near-miss incidents with high potential severity at their institute. Most of these errors cannot be detected by means of pretreatment dose verification, highlighting the importance of IVD.

5.3. Specificity and sensitivity

IVD systems act as binary classifiers where treatments are identified either as positive (alerted) or negative (not alerted). Ideally, a treatment should be classified as a positive only if the actual delivered dose deviation is relevant to the outcome of the treatment; and otherwise it should be considered a negative. In practice, however, treatments are sometimes incorrectly identified: e.g., non-relevant dose deviations classified as positives or relevant dose deviations classified as negatives. False positives lead to unnecessary extra inspection work, while false negatives hide errors not detected by the system. The reasons for incorrect classification are EIVD uncertainties, EIVD limitations and the inappropriate choice of action limits.

Ultimately, the error detectability of an IVD system is expressed in terms of its sensitivity and specificity, i.e., the true positive rate and true negative rate, respectively. EIVD vendors are requested to help the user community determine the sensitivity and specificity of the system for a set of representative clinical situations, for instance through large-scale trials and information gathering initiatives. This includes an assessment of the dependency on treatment site, delivery technique, and/or indicator used. These studies would help in determining optimal action limits to detect errors of a given magnitude and in elucidating the possibilities and limitations of the IVD system, e.g., situations where clinically relevant deviations do not significantly change the recorded signal at the EPID level.

Receiver operating characteristic (ROC) curves can be used to evaluate the ability of IVD systems to correctly classify observed dose deviations and to determine optimal action limits [77]. ROC analysis, however, requires a statistically significant size of error and no-error samples as input. The experimental acquisition of EPID measurements to produce such samples is typically a cumbersome process, which explains why there are only a few studies on the topic in the IVD literature [78–81]. Recently, use has been made of synthetic EPID images to eliminate the need for phantom error introduction and positioning [82]. Another alternative is to model possible errors by introducing modifications in the TPS [83]. Vendors, in collaboration with the clinical community, are requested to promote research activities related to the error detectability of their IVD systems and to facilitate collaboration within a user group. Additional research is also required to investigate the use of alternative measurement analysis techniques, e.g., use of exploratory data analysis, radiomics, and/or machine learning [84–86].

5.4. Online systems

Online EIVD is performed in real time using time-resolved analysis with the aim to interrupt treatment before the total dose has been delivered to the patient [51,52]. There are additional challenges with online EIVD systems such as speed, latency, robustness, specificity, and tolerances for real-time analysis that require further research.

5.5. EPID technology

The main limitation of the use of standard amorphous-silicon EPID technology for *in vivo* dosimetry is the non-water-equivalent response which demands extra commissioning steps and software corrections to effectively model the dose response characteristics of the EPID imager [87,88]. Although research efforts have been made to modify current EPID designs to make them more water-equivalent [89–92], none of these configurations have been adopted for clinical use yet. One of the reasons is that EPID technology developments over recent decades have not been driven by the demands of IVD, but by the needs for improved patient positioning.

5.6. Other IVD systems

In this section, several new developments of IVD in radiotherapy are discussed using systems other than EIVD. These systems need further investigation before they can be used with the required accuracy.

The use of Gafchromic film for *in vivo* entrance dose determination can be advantageous compared to point detectors if a higher resolution is needed. Gafchromic film can furthermore be used to determine the skin dose when introducing a new treatment technique or during total skin electron therapy. Several studies have also shown the usefulness of Gafchromic film during intraoperative radiotherapy, both with electron beams and with low-energy X-ray beams [93]. Improvements regarding film reading characteristics are still needed to increase the accuracy of dose measurements for these types of IVD measurements.

PRESAGE, which is an optically transparent radiochromic dosimeter, has a comparable resolution to Gafchromic film. PRESAGE sheets have the same dosimetric capability as Gafchromic film but are softer and more flexible to conform to the patient's skin, which makes them in principle a valuable tool for IVD [94,95]. However, currently there is only limited experience with PRESAGE sheets.

Recently, Cherenkov imaging has been shown to allow high-resolution, video-rate imaging of radiation delivery to tissue using a gated camera system. The Cherenkov emission can be used to evaluate the surface dose received by the patient in real time. However, the relationship between the video signal and the actual *in vivo* dose is complex. Cherenkov radiation emission in radiotherapy is affected by tissue optical properties (e.g., pigmentation, thickness of tissue), entrance/exit geometry, and imaging angles. Despite the limitations of Cherenkov imaging, several interesting applications have been reported. These include *in vivo* surface dose measurements during total skin electron therapy [96] and imaging during breast treatments to monitor beam shape in real time on the patient's skin throughout the treatment [97].

Recent *in vivo* investigations have shown that short pulses of radiation at very-high-dose rates (several hundred Gy/s) are less harmful to healthy tissue but just as efficient as conventional dose-rate radiation at inhibiting tumor growth. A first patient treatment using this so-called FLASH effect has recently been described [98]. IVD during FLASH radiotherapy is strongly recommended due to the uncertainties in beam calibration and beam monitoring. It seems, therefore, worthwhile to investigate whether existing IVD detectors can be used for this purpose after determination of their dosimetric characteristics in very-high-dose-rate fields [99–101].

IVD should also be accepted as an essential part of translational and preclinical research, where the dose uncertainties are often large [102]. The potential use of EIVD systems in a similar way to that used during patient EBRT treatments has been reported for the verification of small animal kilovoltage X-ray irradiations [103,104], but this needs further investigation.

Finally, it should be noted that there are several EBRT systems where IVD is not used such as the Cyberknife, Tomotherapy, Gamma Knife and ViewRay MR-linac. Also in proton therapy IVD is not used routinely, although various techniques for *in vivo* verification of the delivered dose or the beam range have been proposed and in some cases already clinically investigated [105]. For these EBRT systems new techniques for IVD should be developed.

6. Discussion

This report has documented IVD methods used in EBRT, focusing on EPID-based approaches. The report provides detailed requirements to vendors for overall EIVD system performance, as well as for the EPID imager, image acquisition software, and IVD analysis software. Further recommendations are made for vendors and researchers to improve the understanding and reduce the uncertainties in IVD systems and to estimate the sensitivity and specificity of the system. Finally, the report recommends that automation of all aspects of EIVD is needed to help facilitate clinical adoption, including automation of image acquisition, analysis, result interpretation, and reporting/documentation.

In some cases, requirements are stated without any numerical specifications. This is because specific tolerance values for some of the criteria will depend on the application. A few of these requirements are elementary and are being satisfied by today's technology, while others are not available yet. The goal of this report is to raise awareness for the need of each of the proposed requirements and to prompt users of EIVD systems to ask vendors for details about their fulfilment, using quantitative information whenever applicable. An essential requirement that has been identified for the seamless integration of the different subsystems is the use of open, free and non-proprietary formats and interfaces, e.g. Requirement S3.11. The fulfilment of this requirement would simplify the implementation of EIVD systems and would allow researchers to gain easy access to EPID data in their studies. Another example would be Requirement S3.8 where it is stated that "each integrated image and each cine mode image frame must be tagged with real-time treatment delivery information". But in order to achieve this, linac manufacturers must provide an open interface for access to the raw portal image data and related real-time information which would be beneficial to both potential new vendors of MV acquisition software and researchers.

Task Group 307 (TG307) has been recently formed by the American Association of Physicists in Medicine (AAPM) to review the use of EPIDs for Patient-Specific IMRT and VMAT QA. This task group aims to provide an extensive review on existing EPID products, methods and algorithms for both pre-treatment and *in vivo* dosimetric verification. It is hoped that the proposed requirements in this EBRT IVD report will not only complement the ongoing TG307 work, but will also contribute to raise the awareness of the community about the required capabilities of EIVD systems and inspire further related work. For example, it may lead to recommendations for a set of customer acceptance tests to evaluate and compare the basic performance of EIVD systems to detect errors.

In practice, and owing to the presence of false positives and false negatives, EIVD systems are typically implemented in combination with other patient-specific QA systems. False negatives are of particular importance because they hide relevant errors that are not being detected [82]. To detect these errors, EIVD must be used in combination with image-guided radiation therapy procedures such as CBCT visualization and/or CBCT-based dose calculations. Similarly, the use of linac log files or transmission detectors mounted on the linac head may show additional value in the detection of, or confirmation of the absence of, machine delivery errors. Other QA systems, such as 2D/3D detector matrices or independent dose calculations, can help to discriminate between false and true positives during the inspection of EIVD alerts (see Fig. 2). Table S8 lists several commercial systems that may complement EIVD methods. Finally, note that the sensitivity and specificity of EIVD highly conditions the feasibility of clinical workflows. For instance, if a specific EIVD system is very sensitive to changes in patient anatomy for a specific treatment site, then EIVD assessments could be used to trigger the acquisition of CBCTs in case that these are not acquired daily.

One aspect that has received little or no attention so far is auditing of IVD systems by an external organization, possibly with dedicated phantoms. This may require customized audits for specific EIVD systems. An interesting test could be to combine IVD dosimetry with a regular dosimetric audit when the auditing phantom is irradiated according to the auditing protocol. This would provide information about the agreement between IVD, the audit result, and the TPS for that specific treatment technique. This would only be relevant for IVD methods that reconstruct dose in a phantom.

Finally, it is hoped that widespread clinical use of IVD for EBRT will be significantly accelerated with the guidance of this report.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: I Olaciregui-Ruiz and B Mijnheer declare that their department licensed portal dosimetry software to Elekta Oncology Systems Ltd. for the development of the iViewDose product. This product is currently not commercially available. P Greer declares research collaborations with Varian Medical Systems. B McCurdy declares funded research collaborations on EPID dosimetry with Varian Medical Systems. N. Jornet declares that she is member of the European scientific advisory board of Sun Nuclear. F Verhaegen declares research collaborations and a patent on in vivo dosimetry with Varian Medical Systems.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.phro.2020.08.003.

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Supplementary Material

1. Requirements for EIVD systems

Table S1. Overall EIVD system requirements

#	Name	Description
1	Integration	Automated data flow between EIVD and other systems, e.g., TPS
2	DICOM	If DICOM connectivity, conformance statement
3	Configuration	Supported treatment machine configurations including vendor and model of linac, beam collimation methods/devices, and EPID models
4	Delivery techniques	Support for clinically relevant delivery techniques (e.g., wedged fields, 3D conformal radiation therapy, IMRT, VMAT).
5	Energy	Support for clinically relevant nominal beam energies
6	Gantry	Support in the calculation algorithms for all gantry angle values
7	EPID position range	Support in the calculation algorithms for all EPID positions
8	Field size range	Indicate support for field size range, which depends on EPID size, EPID position range, and source-to-imager distance range
9	Patient accessories	Support in the calculation algorithms for the presence of patient accessories (e.g., scanned or unscanned bolus, immobilization devices)
10	Patient model	Indicate support for anatomical images that can be used as patient model (e.g., CT, CBCT, magnetic resonance imaging [MRI])
11	Analysis	Dosimetric comparison method(s) (e.g., absolute dose, gamma analysis, dose volume histogram evaluation)
12	Automation	Table S5.1-9
13	Uncertainty	Determine the uncertainty of the system for all dose comparison indicators and clinically relevant combinations of delivery techniques and treatment disease sites
14	Error detection	Assessment of the sensitivity and specificity of the system for a set of representative clinical situations

Table S2. EPID imager requirements

#	Name	Description
1	Linearity	< 1% over the entire sensitive area for the range of dose and dose rates used clinic
2	Reproducibility	< 1% over all pixels (assuming a periodic QA program is implemented)
3	Spatial resolution	EPID pixel pitch < 1x1 mm^2 for normal fields and < 0.4x0.4 mm^2 for small and/or stereotactic fields
4	Resistance	High resistance to radiation damage
5	Sensitivity	Allow image formation using only small amounts of radiation
6	Active area	Sufficient to capture all fluence for the maximum field limits deliverable to the patient
7	Frame rate	Allow for EPID frame acquisition without saturation for the highest available dose rate
8	Position accuracy	Reproducible EPID positioning with gantry angle, to < 1 mm of true mechanical isocentricity (or correctable to this tolerance)
9	Backscatter	Mitigate all sources of backscatter, e.g. adding a backscatter shielding

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Table S3. Megavoltage EPID acquisition software requirements

#	Name	Description
1	Image capture	Capture and recording of all dose-related signals throughout treatment delivery
2	Raw image data preservation	Output the raw image data without any corrections applied such as dark field and flood-field
3	Dosimetric calibration	Ability to calibrate the panel for dosimetric use instead of for imaging, e.g. by performing a pixel sensitivity measurement calibration
4	Acquisition modes	Support for image acquisition of integrated single images and cine mode image frames
5	Frame acquisition	Capture all signals between first to last beam pulses in acquired frames
6	EPID scatter	Ability to account for EPID scatter during image formation
7	Backscatter	Ability to account for backscatter contributions to the EPID imager during image formation

8	Meta-data	The acquisition software should add meta-data to the image data which should contain at minimum the following real-time treatment delivery information: - EPID manufacturer, pixel size, number of rows and columns - linac identifier - patient name and medical record number - treatment fraction - arc/field being delivered - beam-on, beam-hold information - beam nominal energy and fluence mode (e.g., flattening filter free) - pixel scaling, if it has been applied, so that the integrated signal can be obtained from the stored values - image acquisition time - collimator and gantry angle - fractional Monitor Unit (MU) - control point - position of the couchtop (translation and rotation) - lateral displacement/position of the EPID - multileaf collimator and jaw positions - respiratory trace signal (amplitude, phase, time stamp), if used - real-time tracking data (fiducial/beacon center-of-mass, time stamp), if used The aforementioned labels/tags must be preserved during upgrades
9	Frame rate	Configurable frame acquisition rates, frame averaging, image gain, and image resolution, to tailor the EPID acquisition to the application, which allows user control over (i) image saturation in flattening filter-free beams and (ii) digital storage size of acquired images, especially for cine mode
10	Gated treatments	Support of integrated or cine image acquisition during gated treatments (i.e., seamless acquisition throughout beam on/off cycles)
11	Open access	Direct, simple, and free open user access to the raw image data and/or the contents of the image acquisition database in nonproprietary format.
12	Open format	Output recorded images in non-proprietary format, e.g. DICOM

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Table S4. EIVD software requirements

#	Name	Description
1	Installation	Straightforward installation, acceptance testing, and commissioning processes

2	Load times	Rapid access and loading (<1 min) of EPID images and any other required image sets and data (e.g., patient anatomical imaging, patient dose matrices, patient treatment plan)
3	EPID dose response	Ability to account for the energy response of the EPID imager in the calculations
4	Patient scatter	Ability to account for patient scatter fluence entering the EPID imager in the calculations
5	Treatment couch	Ability to account for the extra beam attenuation caused by the treatment couch in the calculations
6	Documentation	Detailed documentation of the EIVD software including description of calculation algorithms, image correction methods, etc.
7	Computation	Rapid reconstruction of dose distributions based on EPID images (<1 s for integrated images and <1 min for cine images).
8	Analysis	Rapid analysis and report availability per EPID image, and/or per treatment fraction, and/or per treatment course (<5 s)
9	Online systems	Dose computation and time-resolved analysis must be faster than the EPID acquisition frame rate
10	Configurability	Configurable analysis, comparison settings, and alert process (including alert thresholds and who is alerted)
11	Management	Management and control of EPID commissioning models settings and configuration
12	Persistency	Storage of configuration settings used in the analysis and results in an EIVD database
13	Open access	Direct, simple, and open user access to the EIVD database
14	Open format	Output reconstructed dose distributios in non-proprietary format, e.g. DICOM
15	Data mining	Run statistical, trending, and data mining tools on the database of EIVD analysis results
16	Dose accumulation	For back-projection systems: Deformable modeling tools to accumulate dose per fraction over an entire course of treatment and mapping of any *in vivo* dose estimates to a patient reference anatomy
17	Integration	Access to additional relevant information about the delivery, e.g., CBCT data
18	Regulatory compliance	Software must be developed using medical software development standards for quality management, e.g. ISO13485 or IEC62304

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Table S5. Automation requirements

#	Name	Description
1	Panel deployment	Automatically inform the radiation technologists to deploy the panel
2	Image acquisition	Automatic acquisition of EPID images and related meta-data (see S3.8)
3	Data loading	Automatic loading of plan information, patient anatomical imaging data sets, and reference dose distributions
4	Algorithm inputs	Automatic association of EPID images with the required input data for EPID reconstruction and dosimetric evaluation comparison analysis
5	Batch processing	Automatic run the EIVD software without human intervention after treatment delivery
6	Report	Automatic store the analysis and create a dosimetric report for review
7	Alert management	Automatically raise an alert when deviations are detected outside tolerance levels
8	Workflow	Automatically schedule and supervise remaining actions requiring human intervention
9	Archive	Automatically archive (periodically) patient data to a data-storage device

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13 ## 2. Error detection

Table S6. Error detection by EIVD systems

#	Error
	Machine-related errors
1	Multileaf collimator leaf position/speed
2	Leaf sequencing
3	Collimator angle
4	Beam flatness and symmetry
5	Linac output
7	Gantry angle
	Plan-related errors
9	Leaf attenuation
10	TPS model (geometry model, beam model, output factors, etc.)

11	Dose calculation
12	Delivery of a wrong patient plan
	Patient-related errors
13	Anatomical changes in patient since planning CT
14	Uncorrected patient positioning
15	Anatomical movements during treatment
16	Obstructions from couch support and immobilization devic
17	Missing or wrong bolus material
18	Wrong patient

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17 **3. Commercially available systems**

18 Table S7 lists commercially available systems at the time of writing. The table is partly based on
19 information provided in the upcoming AAPM Task Group-307 report: *The Use of EPIDs for Patient-*
20 *Specific IMRT and VMAT QA*. Table S8 is mainly based on information on the vendors' websites. The
21 authors do not assume any responsibility for the correctness of this information.

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Table S7. Commercially *in vivo* EPID dosimetry systems. None of these solutions supports time-resolved analysis or the ability to produce online assessments.

System	0D/2D/3D	Type	Description
SunCHECK (Sun Nuclear)	2D	Forward (Dose)	PerFRACTION™ Fraction n*:* In-Vivo Monitoring Measures a time-integrated measured portal dose image. Compares to a time-integrated predicted portal dose image from an export of the patient plan and CT. Additional non-IVD method: 3D dose recalculation that uses EPID-measured leaf positions and a log file to create a "delivered" plan for independent dose recalculation. Additional non-IVD method: Compares EPID images of fraction n to 1st fraction with gamma analysis.
EPIgray (DOSIsoft)	Multiple 0D/3D	Back-projection (Direct)	Reconstructs dose at one point from an EPID measurement using planning CT as patient model. Reconstructs 3D dose in a patient by iteration of multiple 0D

			reconstructions. Compares to planned dose distribution.
SOFTDISO (Best Medical)	0D	Back-projection (Direct)	Reconstructs dose at one point at isocenter from an EPID measurement using planning CT as patient model. Compares to planned dose distribution. Additional non-IVD method: Compares EPID images of fraction n to 1st fraction with gamma analysis.
iViewDose (Elekta)	Multiple 2D/3D	Back-projection (Direct)	Reconstructs 2D dose at arbitrary plane from an EPID measurement using planning CT as patient model. Reconstructs 3D dose in a patient by iteration of multiple 2D reconstructions. Compares to planned dose distribution. Note: iViewDose is not commercially available anymore.
Dosimetry Check (LifeLine Software/LAP)	3D	Back-projection (Indirect)	Constructs fluence map from EPID measurement. Back-projects fluence and performs forward 3D dose calculation in patient geometry using planning CT/CBCT as patient model. Works also with ion chamber arrays and diode arrays for input.
Adaptivo (Standard Imaging)	2D	Forward (EPID image)	Measures a time-integrated measured portal dose image. Compares to a time-integrated predicted portal dose image from an export of the patient plan and CT.

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Table S8. Commercially available transmission detector systems. These systems are not considered IVD systems, but can sometimes be used as complementary systems.

System	Type	Description
IQM (iRT)	Linac output monitoring	Transmission detector mounted on linac exit, spatially sensitive signal due to slanted electrode ion chamber. Automatically calculates the expected signal for each individual beam segment. Time-resolved and cumulative signal prediction. Cannot be used to verify patient dose.
Delta^4 Discover (ScandiDos)	Dose calculation in Delta^4 phantom	Transmission detector mounted on linac exit, 4040 disc-shaped p-Si diodes with a diameter of 1 mm. Cannot be used to verify patient dose.
Dolphin (IBA)	2D/3D/4D plan verification	Transmission detector array mounted on linac exit, 1600 matrix ion chambers. Time-resolved recording. Patient present for some procedures (e.g., 3D, 4D dose). No patient error checking.

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