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Review Article

Estimating dose delivery accuracy in stereotactic body radiation therapy: A review of in-vivo measurement methods

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ABSTRACT

Stereotactic body radiation therapy (SBRT) has been recognized as a standard treatment option for many anatomical sites. Sophisticated radiation therapy techniques have been developed for carrying out these treatments and new quality assurance (QA) programs are therefore required to guarantee high geometrical and dosimetric accuracy. This paper focuses on recent advances on in-vivo measurements methods (IVM) for SBRT treatment. More specifically, all of the online QA methods for estimating the effective dose delivered to patients were compared. Determining the optimal IVM for performing SBRT treatments would reduce the risk of errors that could jeopardize treatment outcome. A total of 89 papers were included. The papers were subdivided into the following topics: point dosimeters (PD), transmission detectors (TD), log file analysis (LFA), electronic portal imaging device dosimetry (EPID), dose accumulation methods (DAM). The detectability capability of the main IVM detectors/devices were evaluated. All of the systems have some limitations: PD has no spatial data, EPID has limited sensitivity towards set-up errors and intra-fraction motion in some anatomical sites, TD is insensitive towards patient related errors, LFA is not an independent measure, DAMs are not always based on measures. In order to minimize errors in SBRT dose delivery, we recommend using synergic combinations of two or more of the systems described in our review: on-line tumor position and patient information should be combined with MLC position and linac output detection accuracy. In this way the effects of SBRT dose delivery errors will be reduced.

Stereotactic body radiation therapy (SBRT) has been recognized as an appropriate treatment option for both primary and metastatic tumors in different anatomical sites such as the lungs [1], liver [2], prostate [3] and spine [4]. Furthermore, international recommendations on SBRT delivery are being cited in literature [3,5,6]. An important feature of SBRT is that it delivers high radiation doses to small lesions with short fractionation schemes [7]. Single or few fractions (up to 8) with dose for fraction greater than 6 Gy are commonly used. SBRT requires dose conformity to the target and healthy tissue-sparing. Therefore, geometric and dosimetric accuracy are essential for maintaining SBRT curative power and avoiding dangerous side effects.

Recent studies [8–11] showed that most global health centres are currently delivering SBRT using intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT). Moreover, tracking systems [12,13] and adaptive radiotherapy techniques [14] have recently been introduced for limiting the effects of intra- and inter-fraction anatomical changes [15], respectively. Furthermore, in a severe adaptive radiotherapy scenario, each fraction should be re-planned on a daily basis [16]. All of these sophisticated strategies need to be evaluated.

Potential SBRT-related errors could cause severe injury to patients due to the high radiation dose delivered per single fraction. In this context, proactive risk assessment methods are particularly suitable for investigating the risks of this clinical practice. The Failure Mode and Effects Analysis (FMEA) is a powerful tool for conducting proactive risk assessments in contemporary radiation oncology [17–20]. In the FMEA approach, three indexes are assigned to each failure mode: the occurrence (Occ), severity (Sev) and detectability (Det) ratings. The Risk Probability Number (RPN) is the product of the three scores (RPN = Occ × Sev × Det). In SBRT treatment, severity values greater than the standard RT

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fractionation are expected as a consequence of higher dose per fraction. Therefore, higher detectability in SBRT is required to maintain low RPN values.

Several sources of error may occur in any phase of radiotherapy treatment which may have dramatic consequences, especially if a single high dose fraction is delivered [21]. Standard quality assurance (QA) procedures generally involve periodic equipment and patient specific pre-treatment QA verification. However, periodic equipment controls cannot fully prevent dose delivery errors, and only a few of these errors can be detected by means of pre-treatment QA measurements [22–24]. Therefore, other QA methods should be implemented with the aim of improving the dosimetric accuracy of SBRT treatments [25]. In this review, the recent advances in-vivo measurement methods (IVM) for SBRT are reported. For IVM we consider all of the on-line QA methods used for estimating the actual dose delivered to patients. These methods include: (i) point dosimeters (PD) for acquiring entrance and exit dose measurements along the central axis and (ii) electronic portal imaging device dosimetry (EPID) for 2D and 3D dose reconstruction; (iii) beam fluence measurements with planar transmission dosimeter (TD), (iv) linac log file analysis (LFA), (v) dose accumulation methods based on on-line imaging (DAM).

In particular, PD and EPID can be considered as in-vivo dosimetry (IVD) devices as their results depend both on patient and linac performances. LFA and TD are not sensitive to capture patient related errors such as: anatomical variations, intra-fraction motion and set-up errors. Therefore, these systems are only partially effective in-vivo tools. Moreover, LFA software use the files generated by linac which are insensitive to miscalibration. However, LFA and TD studies were included in this review, as they can be easily implemented and can evaluate the impact of the fluence variation on overall treatment accuracy.

Each method described in this review has its own specificities. A systematic literature search was conducted in order to evaluate the in-phantom and in-vivo performance of these systems. The aim of this study was to compare the accuracy of these IVM methods and their sensitivity to determine the most common and dangerous errors that affect SBRT treatment. The abbreviations used are listed in Table 1.

Table 1
List of abbreviations used in this review.

ABC	Active Breathing Coordinator
Calypso	Electromagnetic transponder-based positioning system
CBCT	Cone-Beam Computed Tomography
COMPASS	2D transmission plane parallel arrays
CTV	Clinical Target Volume
DAM	Dose Accumulation Methods
DAVID	Multi-wire transmission ionization chamber
Delta4 Discover	2D transmission diode arrays
DOLPHIN	2D transmission plane parallel arrays
DVH	Dose Volume Histogram
DynaTrack	Dose Accumulation software
EPID	Electronic Portal Imaging Device Dosimetry
FFF	Flattening Filter-Free
FMEA	Failure Mode and Effects Analysis
IC	Ionization Chamber
IMRT	Intensity Modulated Radiation Therapy
IQM	Integral Quality Monitor: wedge-shaped transmission ionization chamber
IVD	In-Vivo Dosimetry Devices
IVM	In-Vivo Measurement Methods
KIM	Kilovoltage Intra-fraction Monitoring
LFA	Linac Log File Analysis
Magic Plate	2D transmission diode arrays
MLC	MultiLeaf Collimator
MOSFET	Metal Oxide Semiconductor Field Effect Transistor
MOSkin	Real Time MOSFET Device
MRI	Magnetic Resonance Imaging
OAR	Organs At Risk
OSLD	Optically Stimulated Luminescence Detectors
PD	Point Dosimeters
QA	Quality Assurance
SBRT	Stereotactic Body Radiation Therapy
SF	Scintillation Fibre transmission device
SSD	Source–Surface Distance
TD	Transmission Dosimeter
TLD	Termo-Luminescent Detectors
TPS	Treatment Planning System
VMAT	Volumetric Modulated Arc Therapy

Material and methods

Search strategy

A comprehensive search was performed using the 'Pubmed' database. The key words used were: (''in vivo dosimetry'' or ''on line measurement'' or ''dose reconstruction'' or ''dose accumulation'', or ''transmission detectors'' or ''2D arrays'' or "fluence arrays", or ''EPID in vivo dosimetry'' or ''log-files analysis'') and (''radiotherapy'' or ''radiation therapy'' or ''radiation oncology''). Only original papers in English published between 2010 and 2019, as well as the related cited references, describing dose measurement methodologies and evaluation of accuracy and error detection sensitivity were included. Papers on in vivo analysis and SBRT application were also included.

Results

A total of 89 papers were considered in the review. The papers were sub-divided into the following topics: PD (18 papers), TD (14 papers), LFA (7 papers), EPID (39 papers), DAM (11 papers). Each topic was subdivided into sections: (i) a brief introduction with characteristics of each device; (ii) in-phantom accuracy and sensitivity, (iii) in-vivo results, with special focus on SBRT cases. The errors included in this review are reported in Table 2.

Point dosimeters

PDs commonly used for IVD include: diodes, Metal Oxide Semiconductor Field Effect Transistor (MOSFET), Termo-Luminescent Detectors (TLD), plastic scintillators, and Optically Stimulated Luminescence Detectors (OSLD). Each PD needs to be characterized for dose response non-linearity, energy, fading, angle of incidence, and dose rate. Furthermore, beam dependent correction factors, such as source–surface distance (SSD), field size, beam modifiers, or wedge should be considered [26–28]. Small pieces of Radiochromic films can be used to determine entrance skin dose [29]. The main goals reached with PD are: evaluation of delivered dose to the target, the estimation of the radiation doses received by organs at risk (OARs) [26], skin dose and out of field absorbed dose assessment.

Accuracy and sensitivity

Entrance and exit dose measurements are required for target dose evaluation. In particular, the exit dose is used to estimate errors associated with patient anatomical variations and the treatment planning system algorithm [26]. Entrance dose can detect treatment set-up errors and the incorrect use of patient positioning devices [30–33]. In-phantom accuracy of PD used for VMAT and SBRT treatments is reported in Table 3 and ranged from 2% for plastic scintillators to 8% for TLD. MOSkin dosimeters, research devices not yet commercially available, can detect errors in real time. In a phantom study, Alnaghy et al. [34] measured anterior rectal wall dose during prostate SBRT and observed that 75% of

Table 2
Main sources of errors for the stereotactic treatments considered in this review.

Residual set-up errors	Anatomical variation	Plan Computation	Corrupted plan	Intra-fraction motion	Linac miscalibration	Linac variability
Residual or uncorrected patient misalignment after set-up correction with volumetric or planar imaging.	Patient weight changes, internal organ filling variations, lung atelectasis, tumor shrinkage.	Errors arising during plan computation	Plan incorrectly modified during data transfer	Physiological internal organ motions and patient movements on the table during radiotherapy fraction.	Miscalibration of linac output, leafs, collimators or gantry.	Inter-fraction variability of collimator, leafs and gantry positions

Table 3
In-vivo applications of point dosimeters to stereotactic and VMAT treatments.

System	Reference	Test	Accuracy in phantom	Verified plans	Type of treatment	Tolerance	Out of tolerance plans
TLD-700, Harshaw	Lonski P. et al. 2017	out of field dose for single beam	4%	110	SABR	N/A	Systematic underestimation of TPS photon dose was found
TLD GR200A	Dipasquale G. et al. 2014	intracavitary target point dose	8%	61	VMAT	8%	5%
MOSkin	Legge K. et al. 2017	intracavitary OAR point dose	6%	12	VMAT - SBRT	6%	83%
Plastic Scintillator	Cantley et al. 2016	intracavitary OAR point dose	2%	1	VMAT - SBRT	12%	N/A

the measurements were in agreement with treatment planning system (TPS) (with deviations <5%); deviations of up to 12% were found.

In vivo results

The IVD results of PD applied to stereotactic and VMAT treatments are shown in Table 3. Radiation dose in body cavities can be measured in order to estimate OAR doses [35–38]. However, the exact position of PD and its stability over time may prove difficult to monitor [26]. To this aim, in-room cone-beam computed tomography (CBCT) could be used [35,39]. The usual steep dose gradients around the target/OARs could increase the overall measurement uncertainty.

Dipasquale et al. [35] evaluated intra-cavitary and perianal skin doses in patients with anal or rectum cancer treated with VMAT using TLD. An 8% dose agreement was observed between measured and planned doses. Cantley et al. [38] used a plastic scintillating detector placed in an endorectal balloon which provided real-time in vivo dosimetry for prostate SBRT treatment. Measured doses were within 6% of the expected dose with deviations for single fractions up to 51%. Cho et al. [40] reported Radiochromic measurements versus TPS prediction of near surface dose and Monte Carlo calculations with differences of up to 69%. Legge et al. [37] used MOSkin detectors in order to obtain real time in vivo measurements of anterior rectal wall dose during prostate SBRT boost treatments. The authors found that uncertainty in the position of the MOSkin detector was the major source of discrepancy, as the PD was placed in a high dose gradient region. The mean difference between planned and measured point doses for all VMAT arcs considered over the entire course of treatment was: 9.7% ± 3.6%.

Riegel et al. [41], using OSLDs, investigated IVD over eleven-thousand verifications and reported excellent mean agreement (0.3% dose difference) but high standard deviations (12% for IMRT and 13% for VMAT).

Out-of-field dose assessment

Another application of PD is the out-of-field dose assessment. Studies on the use of LiF-TLDs and ionization chamber (IC) [42,43] were carried out to compare measurements with TPS dose calculations. Lower accuracy for photon dose calculation at increasing distance from the isocenter was observed. Higher out-of-field doses were correlated with some gantry angles and couch positions.

Evaluation of peripheral dose for flat and flattening filter-free (FFF) photon beams in SBRT was carried out by using a Farmer type IC. Removal of the flattening filter resulted in lower peripheral doses [44].

Transmission detectors

TDs are placed between the patient and the radiation source, thus allowing for dose monitoring and multileaf collimator (MLC) position performance monitoring.

Current TDs use various ionization chambers: The DAVID multi-wire transmission ionization chamber (PTW-Freiburg, Germany) [45,46], 2D plane parallel arrays (COMPASS [47] and DOLPHIN [48] (IBA Dosimetry, Germany)) and the large wedge-shaped ionization chamber (integral quality monitor (IQM) (iRT Systems GmbH, Germany)) [49,50]. 2D diode arrays have also been developed: Delta4 Discover (ScandiDos Sweden), Magic Plate [51]. Moreover, a scintillation fibre (SF) detecting device has been tested [52]. The photon beam perturbation of TD was investigated by evaluating beam transmission, the increases in surface dose, the percent depth dose (PDD) and profile variations. Transmission factors should be characterized for all energy sets and conventional and FFF beams.

For all systems except for COMPASS and DOLPHIN systems, the perturbation effect can be considered by adding a transmission factor to the TPS. Due to the beam perturbation effects, COMPASS can no longer be purchased, and DOLPHIN is only currently sold for pre-treatment QA but not for IVD.

Accuracy and sensitivity

DAVID proved to efficiently and accurately detect a wide range of clinical and artificial errors [45]. The sensitivity of the IQM to leaf bank and single leaf errors is higher for smaller than for larger fields [53,54]. Furthermore, the device is capable of detecting small delivery errors in MU and leaf positions [53,54]. Diode array's detection accuracy and precision for MLC positioning errors with both static and dynamic delivery are within 0.7 mm and 1.2 mm, respectively [55]. In comparison, the wire ion chamber is able to detect leaf position errors of 1.0 mm in static fields and 2.0 mm in IMRT fields [45]. SF can detect leaf position errors of 1.0 mm in IMRT fields, although only 2.0 mm paired-leaf errors were

detectable [52]. The wedge TD can detect leaf positions errors of 1.0 mm in static fields and 3.0 mm in IMRT fields [56].

Marrazzo et al. [53] found a good correlation between IQM own and Dose Volume Histogram (DVH) metric. Therefore, clinical action levels can easily be defined. Unfortunately no detection capability data is currently available for the COMPASS and DOLPHIN systems.

In vivo results

Clinical experience was reported only in the study by Poppe et al. [46]. Two clinically relevant discrepancies were detected: one was due to the de-calibration of the upper collimator block, the other error occurred when the plan was imported into the record and verify system. Even if Poppe et al. consider the DAVID system to be optimal, it is no longer commercially available.

The performances of the IQM and DOLPHIN systems were only evaluated for pre-treatment verification from a clinical perspective [53–58] but no clinical experience was reported.

Log file analysis

The machine log file analysis was used to verify dynamic and segmental IMRT [59] delivery and for patient-specific IMRT and VMAT QA [60–62]. All of these tools were designed to evaluate the discrepancies in IMRT and VMAT delivery after treatment. Log file-based dose reconstruction also enables evaluation of the dose distribution in the patient's anatomy. Tyagi et al. [63] developed a real time dose monitoring and dose reconstruction tool to identify and quantify sources of errors during patient-specific VMAT delivery, with which they quantified the delivery characteristics of various standard fractionation and SBRT VMAT plans.

Accuracy and sensitivity

Neal et al. recommended that log file-based methods without independent confirmation of the log records should be used with caution [64]. They suggested a frequent verification of MLC positions through independent means such as EPID is a necessary precondition to trust log file data.

In vivo results

Hirashima et al. [65] continuously monitored mechanical errors and their impact on dose distributions during VMAT using log files acquired from 2 patients with skull base brain tumour and from 13 prostate cancer patients. Dosimetric uncertainties caused by mechanical errors occurred at a frequency below 1.0% in the clinical target volume (CTV) for skull base brain tumors and prostate cancer. The largest dosimetric deviation was observed in an OAR; however, the resultant error in the accumulated daily delivered dose distribution, in the patient with the largest deviation, was up to 1.6% for all dose-volumetric parameters compared with the planned dose distribution.

Electronic portal imaging device dosimetry

There are two approaches for using EPID in IVD: the forward (2D transmission image comparison at the position of the EPID) or the back-projection method (dose reconstruction using transmission images, point dose, 2D, and 3D doses). In the first method, the measured EPID signal is compared with the planned exit fluence projected to the EPID [66,67]. In the second method, the primary dose is back-projected to body planes parallel to the EPID for each beam/bin in order to determine the dose received by a patient at either a point [68–73] or a plane [74] or over a volume within the patient [75–81]. The forward method is relatively more straightforward, while the back-projection method has the advantage of generating a 3D inpatient dose distribution, which can be compared with the dose distribution on the planning CT [82]. Moreover, with the use of CBCT, EPID IVD can take into account daily anatomical changes [83]. Also in this case, real time and 4D IVD algorithms [84,85] for lung tumor radiotherapy [86] have been implemented.

Accuracy and sensitivity

In order to test the sensitivity and accuracy of both EPID-based in-vivo dosimetry methods, several studies have been conducted using the forward and back-projection method, with homogeneous and heterogeneous phantoms [84–93] during which various errors were deliberately introduced for evaluating the performance and identify the limitations of on-line EPID-based dosimetry. EPID proved to have high sensitivity in detecting anatomical variations and linac parameter errors such as leaf position, collimator gantry position errors. However, EPID sensitivity in detecting set-up and inter-fraction patient variations proved to be poor in some anatomical sites, especially those characterized by tissue homogeneity like the pelvis. In an anthropomorphic phantom study Mijnheer et al. [93] detected an intentional shift of 2 cm in the head and neck region, while no shift was detected in the prostate or lungs. In the same paper, 1 cm phantom thickness variations were detected in all anatomic regions. A recent study by Olaciregui-Ruiz et al. [90] showed that error detection sensitivity also depends on the type of metric used for the analysis and on the anatomical site treated. The sensitivity of EPID to capture intra-fraction respiratory variations was assessed in the study carried out by Moustakis et al. [94] in a moving phantom. In this paper a γ metric of 1%/1mm was used to determine the interplays effect and no errors were detected with 3%/3mm and 2%/2mm metrics.

In vivo results

Most in vivo results were obtained in mono institutional large scale studies [95,96,68,97]. Fig. 1 shows the percentages of out of tolerance plans along the type of errors along various studies.

All of these studies indicated that the IVD software, especially in the γ-like analysis of EPID images, was able to identify patient morphological changes due to weight loss, tumor shrinkage and/or different rectum or bladder filling for CT simulation. In these

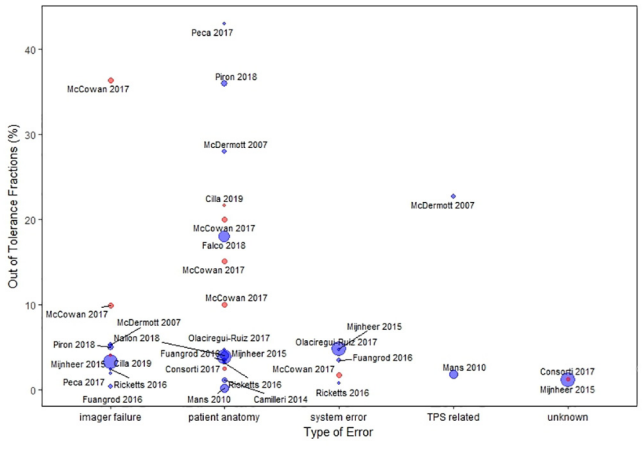

Fig. 1. Out-of-Tolerance fractions vs type of errors in various EPID-based in vivo dosimetry studies. The size of the dots indicates the number of fractions analyzed. SBRT-specific studies are colored in red. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

cases, when significant and non-episodic anatomical changes are observed, EPID-based IVD provides useful warning for an eventual adaptive strategy. Ricketts et al. [98] proposed a decision-tree workflow for EPIgray: any potential patient anatomical changes such as patient positioning errors, bowel gas, weight loss/gain, and bladder filling were investigated if the IVD measurements were outside the established tolerance levels. Preliminary data suggested that different action levels may be required for different anatomical sites.

SBRT in vivo studies

Some publications reported EPID-based IVD results for SBRT. A recent review by McCurdy and McCowan [25] presented the technical aspects of IVD for lung SBRT, placing special emphasis on EPID-based IVD ability to identify errors that would not have been detected using other common QA systems. McCowan et al. [79] investigated using the continuous acquisition mode of the EPID (cine mode) and Monte Carlo based dose reconstruction algorithm for SBRT VMAT delivery in the liver, lungs and spine. The cine acquisition mode was also investigated by Lin et al. for 4D patient dose reconstruction [71].

Consorti et al. [99] reported data obtained from 15 patients (160 tests) and found clinically relevant discrepancies in three patients: a set-up error, a morphological change in a patient identified by CBCT image analysis and a third discrepancy that was not fully justified. Overall, the maximum 5% tolerance in the γ-like analysis was reported for this kind of treatment. Cilla et al. [100] described their clinical experience with EPID-based IVD for lung metastases treated with VMAT technique. Data were collected for 10 patients (50 tests); 8 patients were treated with deep inspiration breath-hold techniques using the Elekta Active Breathing Coordinator (ABC) and 2 patients were treated in free-breathing using an abdominal compressor. Using a 3%(global)/3 mm criteria, the results reported a high level of dose delivery accuracy for the patients treated with the ABC spirometer. Relevant discrepancies were only observed for the two patients treated without ABC, mainly due to the dose blurring effect caused by residual respiratory motion.

Yedekci et al. [101] evaluated the feasibility of EPID 3D in vivo dosimetry for SBRT treatments of ten prostate cancer patients. In addition, a pelvis phantom study was performed to investigate the EPID detectability of several error scenarios as dose calibration, set-up and MLC inaccuracies and patient anatomy variations. Clinical results were excellent with a gamma passing rate equal to 96%. However, phantom measurements reported that positional errors up to 2 cm can escape from detection, suggesting that EPID transit dosimetry for pelvic treatments must be used in combination with image guided radiation therapy procedures.

Various strategies are currently used for producing instantaneous in-vivo results, e.g. to detect serious real-time errors during beam delivery as they occur. To date only two clinical experiences of real-time EPID-based IVD have been reported. Woodruff et al. compared measured and predicted portal dose images, and detected significant dose delivery errors in head and neck and in pelvic IMRT and VMAT treatments [85]. A current research project on real-time EPID-based 3D dose reconstruction [102], is focused on combining an online dose verification system with a linac halting mechanism in cases of major discrepancies. Compatibility between EPID IVD and linac-MRI hybrid machines has been proven by Torres-Xirau and co-workers [103,104].

Dose accumulation methods

Dose accumulation methods are computational tools that estimate the dose absorbed by target and surrounding OARs during dose delivery. These methods take tumor and patient positions and the movements of the linac into account: leaf, gantry and collimator positions.

Three elements are required: (i) a tracking system to monitor patient and target positions, (ii) a linac machine status monitoring system, and (iii) a dose computation tool that reconstructs and accumulates the dose during the fraction.

The tracking systems are usually imaging devices or implantable electromagnetic transponders. The imaging modalities adopted were kV X-rays imaging or MRI. The system Kilovoltage Intrafraction Monitoring (KIM) [105], was used to monitor the position of the radiopaque markers placed in the PTV in the liver [106,107] and prostate [108]. Tumor and patient positions were tracked by MRI for abdominal and liver SBRT in the simulation studies conducted by Glitzner et al. [109] and Fast et al. [110] respectively. Signals from the electromagnetic transponder-based positioning system (Calypso) were used for reconstructing prostate position [111] and liver trajectories [112,113]. The lung tumor motion trajectories were reconstructed using data acquired with 4D Computed tomography in the study by Kamerling et al. [114].

Several linac beam monitor systems were proposed: Ravkilde et al. developed an in-house add-on to iTools Capture software (Varian) [107] for monitoring continuous parameters, such as gantry angles and leaf positions. In the study by Glitzner et al. [109], machine parameters were logged using a 40 ms sampling interval.

The tracking software DynaTrack connected to linac and TPS receives actual target positions and MLC apertures independently at 25 Hz, and it is responsible for dose accumulation [114,115]. Linac log files containing information on leaf positions, gantry angles, couch shifts and delivered monitor units were used by Keall et al. [108], Worm et al. [112] and Poulsen et al. [113]. In [106] the dynamic linac status was not tracked, but the TPS generated plan was used for dose computation, assuming that plan variations were negligible.

Accuracy and sensitivity

The accuracy of dose accumulation methods in phantom studies has been demonstrated by many authors. In the study conducted by Poulsen et al. [113], 99% of points with gamma index (GAI) < 1 at 2%2/mm were obtained, against film dosimetry in moving lung phantom, Ravkilde et al. [107] compared the computational method with Delta4 dosimeter measurements in static and dynamic configuration, obtaining an area under the ROC curve of approximately 0.925.

In-vivo results

The impact of MLC tracking for margin reduction was evaluated in simulation studies for prostate [111,115] and lung [114]. Two kidney cases were simulated using 4D-MRI imaging of volunteers by Glitzneret et al. [109]. The accumulated dose revealed local dose variations ranging from −2.3 Gy to +1.5 Gy in the PTV and high local dose errors ranging from −2.5 to +1.9 Gy in the adjacent organs at risk. Poulsen et al. estimated a mean dose reduction in CTV $D_{95\%}$ caused by respiratory motion of approximately 6% in liver SBRT in 18 fractions belonging to 6 patients [106]. In the study carried out by Keall et al. [108] dose accumulation was used to validate offline MLC tracking of 40 fractions of 8 prostate SBRT treatments with KIM. Worm et al. [112] reconstructed 45 liver SBRT treatment fractions with MLC tracking using the Calypso system.

Discussion

In this study several IVM devices and methods and their detectability abilities for SBRT treatments were reviewed and crit-

Table 4
Comparison of the sensitivity of the various systems in detecting the errors listed in Table 2.

	Residual set-up errors	Anatomical variation	Plan Computation	Corrupted plan	Intra-fraction motion	Linac miscalibration	Linac delivery variability	Out of field dose assessment
Point Dosimeters	Reported by Noel et al. [30]; Fiorino et al. [31]; Higginns et al. [32] using entrance dose.	Potentially sensitive using exit dose, but never reported in literature	Potentially sensitive using exit dose, but never reported in literature	Potentially sensitive but never reported in literature	Limited sensitivity due to lack of spatial information reported by Legge et al. [37]	Potentially sensitive but never reported in literature	Not sensitive	Reported by Lonski et al. [42] using TDL and by Covington et al. [43] and Kragl et al. [44] using ionization chamber
Transmission Dosimeters	Not sensitive	Not sensitive	Not sensitive	Reported by Poppe et al. [45] using DAVID	Not sensitive	Collimators position miscalibration reported by Poppe et al. [44] using DAVID	Reported By Goulet et al. [52]; Marrazzo et al. [53] ; Razinskas et al. [54]; Li et al; Giglioli et al. [56]	Not sensitive
Log File analysis	Not sensitive	Not sensitive	Not sensitive	Potentially sensitive but never reported in literature	Not sensitive	Not sensitive	Reported by Hirashima et al. [65]; Neal et al. [64] reported erroneous informations stored in log files	Not sensitive
EPID	Reported by Zhuang et al. [88], Esposito et al. [89]; Olaciregui-Ruiz et al. [90]; Li et al. [91]; Mijnheer et al. [92]	Reported by Cowan et al. [80]; Foundrog et al. [84]; Olaciregui-Ruiz et al. [90]; Mc Mans et al. [76]; Bojechko et al. [92] Mijnheer et al. [93]	Reported by Mans et al. [76]	Reported by Mans et al. [76]	Reported by Moustakis et al. [94]	Reported by Zhuang et al. [88]; Esposito et al. [89]; Li et al. [91]; Bojechko et al. [92]	Reported by Hsieh et al. [87]; Zhuang et al. [88]; Esposito et al. [89] ; Bojechko et al. [92]	Not sensitive
Dose Accumulation Methods	Reported by Poulsen et al. [103]; Ravkilde et al. [106]; Keall et al. [107] ; Fast et al. [109]; Kamerling et al. [110]	Reported by Poulsen et al. [103]; Ravkilde et al. [106]; Keall et al. [107]; Fast et al. [109]; Kamerling et al. [110]	Potentially sensitive but never reported in literature	Potentially sensitive but never reported in literature	Reported by Poulsen et al. [105]; Ravkilde et al. [106]; Keall et al. [105]; Fast et al. [109]; Kamerling et al. [110]	Not sensitive	Potentially sensitive, depending on the linac monitoring system used	Not sensitive

Table 5
Comparison of the strengths and weaknesses of the in-vivo devices described in the review.

	Point dosimeters	Transmission Dosimeters	LOG Files Analysis	EPID	Dose Accumulation Methods
Pros	Very well established use	Real time monitoring of Linac status	Fast and simple assessment of linac reproducibility	Hardware already in the linac room	Assessment of intrafraction movements
	Sensitive to linac and Patients errors	Possibility to monitor all fractions;	Sensitive to plan corruption errors	Sensitive to linac and patient errors	Possibility to use for QA of tracking systems
Cons	Entrance and Exit dose not defined in Arc treatments	Insensitive to patient related errors;	Insensitive to linac miscalibration	Low sensitivity to detect set up errors	Use of log files instead of independent linac status monitoring
	Lack of spatial informations	Introduce a beam perturbation	Insensitive to patient related errors	Low specificity to detect errors is reported	Commercial systems not available

ically analyzed. Errors arising during SBRT treatments could cause severe injury to patients due to the high radiation dose delivered per single fraction.

Determining the optimal IVM method for performing SBRT treatments would reduce the risk of errors that could compromise treatment outcome.

All the devices described in this review help to estimate the actual dose absorbed by the patient during a fraction of radiation therapy. We made a distinction between methods that can be considered IVD and methods that should be considered "only" IVM. By IVD we intend the methodologies that provide results that depend both on linac performance and patient-related problems (such as anatomy, set-up, intra-fraction movement). An IVD system must be able to capture errors due to equipment failure, dose calculation errors, patient positioning errors, and patient anatomy changes. Therefore, IVD methods include merely PD and EPID. All other systems lack one between patient dependency and linac delivery assessment. The smart combination of two or more IVM methods could produce a complete IVD method if both patient and linac issues are simultaneously taken into account (i.e. combination of TD and SAM based on on-line imaging).

Table 4 reports and compares the ability to detect the most common and dangerous errors that could occur during the delivery. The strengths and weaknesses of each method are shown in Table 5. PD and EPID systems have proved capable of detecting the main sources of errors. However, both systems have some limitations.

PDs measure the integral dose from small volumes; therefore they are unable to detect the steep dose gradients that are required in SBRT treatments. Furthermore, the uncertainty of detector position reduces device sensitivity. For these reasons, published studies usually considered a tolerance level of approximately 8–10% (Table 3). In rotational radiation therapy, the entrance dose cannot be defined, and PDs cannot be used to estimate target dose. In this case they can only be used to measure radiation dose in body cavities or for out-of-field dose estimation. EPID is the most used IVD system as it is already mounted on all linacs as a portal imaging device. Although EPID can detect many potential delivery errors, including intra-fraction movements, sensitivity analysis has only been used to validate a few types of software [89–94]. Low sensitivity for detecting positioning errors such as rigid body and rotational motion was observed. Moreover, published IVD results revealed low specificity of EPID-based software in detecting clinically relevant errors: Mijnheer et al. [95] found a number of out-of-tolerance (OTL) flagged fractions of 31%, which would have been reduced to 15% by improvement of the choice of the dose reference point and the use of bolus material. Mc Cowan et al. [80] found that after optimized EPID acquisition, the OTL decreased from around 20% to 9%.

TDs showed high sensitivity in monitoring linac delivery. Minimal monitor unit or leaf and collimator variations were intercepted by these devices [53–58]. However, protection against linac variations are generally provided by the linac manufacturers. TDs can provide an additional check of the linac machine status and protect against calibration errors. TDs cannot detect errors due to the patient such as incorrect set-up, intra-fraction movements and anatomical deformations. The same error detection blindness is shared by LFA software. Moreover, log files are generated by linacs, therefore errors arising from output or collimator mis-calibration cannot be detected by this software. Indeed, LFA only detected small disagreements between planned and delivered dose distributions [60].

DAM could prove useful for evaluating intra-fraction movements and quality assurance of MLC tumor tracking systems. However, they have the same disadvantages as LFA systems because instantaneous MLC and gantry position data are usually extracted from log-files. Even worse, in some cases leaf, collimator and gantry positions used for dose re-computation are taken from RTplans, assuming perfect delivery. In order to increase error detectability, the actual dynamic linac status should be used in these types of software. A combination of EPID, LFA and dose computation methods is used in PerFraction software (Sun Nuclear, Melbourne FL, USA) [116], which provides dose re-computation in CBCT, using scans of actual pre-treatment patient anatomy [116].

The main challenge posed by the routine clinical use of IVD devices is that there are no universally accepted tolerance limits and action levels for each device. However, the AAPM TG-218 report [117] provides recommendations for methodologies and tolerance limits in patient-specific IMRT QA.

This methodology was applied for analyzing IVD in one study conducted on an EPID-based real-time delivery verification system [118] and it was also used in the study carried out by Olaciregui-Ruiz et al. [90]. SCP can potentially be used to establish the tolerance limits and action levels of all IVD devices regardless of each specific dosimetric test.

Analysis of incident reporting system data has quantitatively demonstrated that IVD is a highly effective addition to the commonly used quality assurance procedures, providing greatly improved error sensitivity and is also deemed to be one of the most effective checks. Ford et al. [17] found that combining EPID IDV with safety checks performed by technicians, oncologists and physicists resulted in 93% effectiveness in error detection.

In conclusion

i. In addition to common pre-treatment QA programs, including the commissioning of new devices and techniques, IVM increases dose delivery confidence levels by detecting the errors that can occur at any time and cannot be found with monthly or weekly QA periodicity. Variations in linac status caused by periodic maintenance errors, or lack of maintenance, or changes in the RTplan for new schedules or adaptive purposes could not be detected by periodic QA before treatment effectiveness was compromised.
ii. The introduction of the adaptive radiotherapy approach, based on how the patient responds or changes throughout the treatment process and the use of tracking systems,

require the on-line measurement of the actual dose absorbed by the patient.

iii. Ideal IVD system for SBRT application should operate in real time and interrupt the treatment before relevant errors can compromise treatment outcome. However, to the best of our knowledge this type of system does not yet exist.

iv. For optimal error detection, on-line information on tumor and patient position should be combined with information on MLC position accuracy and linac output. As most of the Linacs used for SBRT treatments are already equipped with EPID, it seems advisable to combine EPID IVD with common pre-treatment QA and CBCT kV imaging. The synergistic effect of these quality controls can detect errors caused by anatomical changes, set up delivery errors and intra-fraction motion. However, the sensitivity of EPID IVD in detecting specific errors should be carefully tested by each user before routine clinical use. The inclusion of DAM based on on-line imaging could further reduce dosimetric uncertainties caused by intra-fraction motion.

Conflict of interest

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