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Review Article

In vivo dosimetry in brachytherapy: Requirements and future directions for research, development, and clinical practice☆

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ABSTRACT

Brachytherapy can deliver high doses to the target while sparing healthy tissues due to its steep dose gradient leading to excellent clinical outcome. Treatment accuracy depends on several manual steps making brachytherapy susceptible to operational mistakes. Currently, treatment delivery verification is not routinely available and has led, in some cases, to systematic errors going unnoticed for years. The brachytherapy community promoted developments in *in vivo* dosimetry (IVD) through research groups and small companies. Although very few of the systems have been used clinically, it was demonstrated that the likelihood of detecting deviations from the treatment plan increases significantly with time-resolved methods. Time–resolved methods could interrupt a treatment avoiding gross errors which is not possible with time-integrated dosimetry. In addition, lower experimental uncertainties can be achieved by using source-tracking instead of direct dose measurements. However, the detector position in relation to the patient anatomy remains a main source of uncertainty. The next steps towards clinical implementation will require clinical trials and systematic reporting of errors and near-misses. It is of utmost importance for each IVD system that its sensitivity to different types of errors is well understood, so that end-users can select the most suitable method for their needs. This report aims to formulate requirements for the stakeholders (clinics, vendors, and researchers) to facilitate increased clinical use of IVD in brachytherapy. The report focuses on high dose-rate IVD in brachytherapy providing an overview and outlining the need for further development and research.

1. Introduction

Significant recent developments in high dose-rate (HDR) brachytherapy include the use of image guidance [1], new applicators [2,3], and dose calculation algorithms [4–6]. These innovations have led to improved treatments that have been shown by recent studies to have excellent clinical outcomes [7,8]. However, because of the manual steps in the treatment process and the high dose gradients, brachytherapy is susceptible to operational mistake. According to the International Commission on Radiological Protection [9], more than 500 separate brachytherapy incidents around the world had been reported by 2004. The lack of proper monitoring systems has led, in some cases, to systematic incidents going unnoticed for years and affecting many patients. Recent incidents involving large numbers of patients have been reported

☆ 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 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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in the Netherlands and Canada [10,11]. Moreover, the number of reported incidents is most likely an underestimate because treatment verification is currently not routinely available. There is, therefore, a critical need for systems that are capable of verifying brachytherapy treatments.

The lack of proper brachytherapy treatment monitoring has received particular attention over the last decade. In 2013, Tanderup et al. [12] gave an overview of the status of detectors for brachytherapy at that time and a direction for the future of *in vivo* dosimetry (IVD). *"IVD is defined as 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, applicator positioning errors, and patient anatomy changes."*

The goal of IVD in brachytherapy can be defined on three levels: 1) Catch large deviations from the treatment plan that can affect the clinical outcome of the treatment. If real-time IVD is performed, this may enable an interruption of the treatment and prevent errors if the uncertainty of the used IVD system is low enough; 2) Keep a record of smaller deviations from the treatment plan that violate some threshold, enabling interfraction adaptation; 3) Provide an estimate of the real delivered dose for the patient record.

IVD measurements are normally compared to the treatment plan, and it is important to realise that deviations observed between planned and measured dose can both stem from deviations between the planned and delivered dose (clinical effect) or between the delivered and the measured dose (measurement uncertainty). The uncertainty of a source tracking system limits which deviations between the delivered and planned dose can be detected as will be shown in Section 5. The true delivered dose to the patient is unknown and lies within measurements uncertainties. If the measurement uncertainties are infinitesimally small, measured and delivered dose would be equivalent.

Multiple initiatives and approaches to IVD in brachytherapy were reported. However, despite promising results in phantoms, very few of the systems have been used clinically. The aim of this report is to formulate requirements for the stakeholders (clinics, vendors, and researchers) to facilitate increased clinical use of IVD in brachytherapy. While previous efforts focused mainly on detectors, subsequent developments in IVD have shifted the focus of the field towards requirements for the entire IVD workflow.

2. Materials and methods

While this report does not constitute a formal systematic review, we performed a thorough literature review to identify the methods employed in clinical trials and novel methods currently in development (phantom studies). Articles were identified performing a PubMed search using the term *brachytherapy combined with in vivo*, *dosimetry* or *measurement*. Articles describing phantom measurements performed with time-integrated detectors were disregarded whilst all clinical trials were included. Additional articles were identified based on the reference lists of the selected papers.

3. Deviations between delivery and treatment plan and their impact on dose and local tumor control

3.1. Deviations between delivery and treatment plan in brachytherapy

This section will summarize the types of deviations between delivery and treatment plan that can occur in brachytherapy and identify errors that could be identified by IVD. For a more comprehensive list see Supplementary material A. Potential errors are numerous, and many of them have their own dosimetric signatures. The most common types of deviations between delivery and treatment plan in brachytherapy stem from misplacement of the source (see 3.2), deviations in source dwell time, anatomical changes or application of incorrect source-specific parameters (e.g., reference air kerma rate). Developers of IVD systems should be aware of the sensitivity and specificity of their systems to certain errors. The limitations of each technology should be quantified and provided by the manufacturer so that the end user can select which equipment is most suitable for the intended clinical application.

Judgement of the severity of deviations between delivery and treatment plan should be based on the clinical impact in the delivered dose. The report of AAPM Task Group (TG) 100 classified errors according to their severity [13]. Dose errors between 5% and 10% are classified as a *wrong dose distribution* whilst errors that have a high probability to cause severe adverse effect are classified as *very wrong dose distribution*. *Wrong location for dose* and *very wrong location for dose* refer to errors smaller and greater than 5 mm, respectively. The *very wrong* classification can cause life-threatening complications, while *wrong* refers to an increase of the probability of unacceptable consequences for the treatment. These definitions have been supported for brachytherapy by clinical studies. Dose-effect studies on prostate and cervical cancer brachytherapy have shown how certain dose-volume histogram (DVH) metrics correlate with local tumor control [14,15]. An unintended decrease of 10% in brachytherapy dose can cause a decrease of 2–4% in the probability of local tumor control [16]. A localized dose boost (from 75.4 to 83.4 Gy) showed an increase of more than 12% in the probability of tumor control in prostate cancer cases [17,18]. Therefore, dose errors beyond 10% can have significant clinical effects.

3.2. Impact of source position deviations

The relation between source position deviations and target dose has been investigated in several studies. In locally advanced cervical cancer, target dose (CTV D_{90}) changes by an average of 2% per millimeter (systematic) offset of the brachytherapy implant [16]; in general, an accuracy of 5% or 10% was achieved by controlling the implant geometry within 2.5 mm or 5 mm, respectively. Simnor et al. [19] showed a decrease of up to 32% in the PTV dose due to catheter displacement (range 0–26 mm) between consecutive fractions. Poder et al. [20] showed that needle offsets between 2 and 6 mm for three or more needles in a high-dose rate (HDR) prostate treatment led to significant changes (>10%) in the relevant DVH metrics. Buus et al. [21] reported that overall migration of an HDR prostate implant by 3 mm and 5 mm led to decreases in prostate gland dose of 5% and 10%, respectively. The impact of a single needle offset or random offset is significantly less than that of overall migrations or offsets [22]. The impact of geometric deviations on the target dose depends on the treatment site and patient anatomy and can be more significant when boosting smaller volumes, as, for example, in focal boosting with prostate brachytherapy.

3.3. Detection sensitivity and false alarms

An important feature of an IVD system is its ability to identify errors with clinical impact and trigger an alarm. However, it is equally important to keep the number of false alarms (see Section 5.1) low to avoid unnecessary additional treatment time and discomfort for the patient. The balance between detection of errors with clinical impact and avoiding false-positive alarms depends on the action levels discussed in Section 5.1. Lower action levels may require more staffing to resolve a larger number of events, whether false alarms or true errors.

4. Methods for IVD

The goals of IVD include providing the clinical staff with a measure of treatment progression and enabling fast intervention in case of clinically relevant errors. This has traditionally been done through measurement of the delivered integrated dose at specific points. However, the emergence of new detectors that can provide information on the delivered dose rate for each dwell position has opened new avenues

towards more sophisticated approaches and levels of feedback. Feedback on treatment progression is defined as measures based on the IVD reading that are presented to the clinical team or to an automated system to decide whether the treatment is progressing according to expectations. "Feedback levels," thus, can be of very different nature as shown in Fig. 1. The figure shows that the more clinically relevant a feedback is the more complex it is. Adding complexity and different measurements will add additional uncertainties [23]. Therefore, the higher the feedback level, the higher is the demand for low uncertainties in the individual components. A higher level of feedback is therefore not necessarily better than a lower feedback level, if the added uncertainty is too high. An increasing number of studies have reported the advantages of time-resolved IVD and the possibility of using source tracking, i.e., determining source dwell times and positions based on measurements. This is advantageous, as positional and temporal offsets are the two major contributors to deviations between delivery and treatment plan, and the entire 3D dose distribution can be reconstructed.

4.1. *Time-integrated point/multipoint dosimetry*

Measurement of the total integrated dose in a single point or a limited number of points is the simplest and by far most widely used form of IVD [12,24,25]. Clinical applications of point dosimetry have shown large deviations between measurements and planned values (Section 4.3). The main reason for these deviations is the steep dose gradient, which requires precise positioning of the detector. Even if a high dosimetric accuracy is achieved, the technique is limited by the fact that the accumulated dose at a single point is often dominated by a few nearby dwell positions, while dwell positions further away may contribute less than a percent of the total measured dose. Deviations between measurements and treatment plan related to dwell positions far away from the detector, therefore, typically go unnoticed, even though they can have a large local dosimetric impact. Another disadvantage of this method is that detection of deviations is only possible after delivery, so real-time interruption and correction of the treatment is not possible.

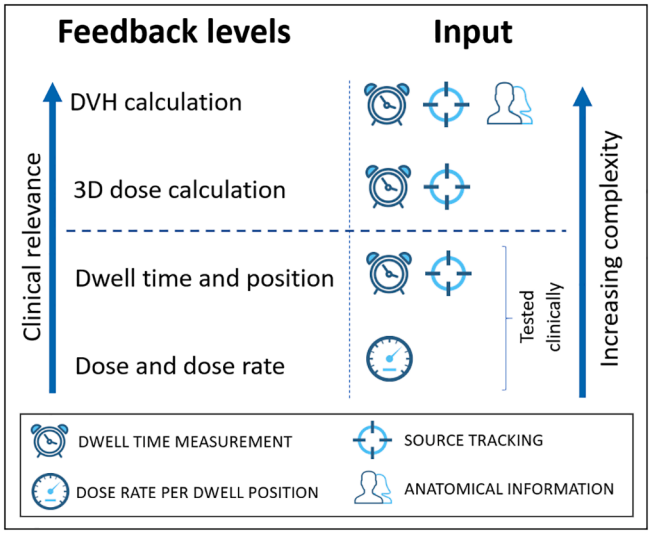

Fig. 1. Feedback levels and corresponding necessary measurement inputs. The horizontal dashed line indicates the current level reached in clinical practice and research. Note that anatomical information is not necessary for dwell time verification. Source tracking can only be performed in relation to the detector. 3D dose reconstructions can be calculated assuming the patient geometry does not change between treatment planning and delivery. However, accurate source positioning relative to the patient anatomy is always desirable, and a lack of anatomical information limits the type of deviations from the treatment plan that can be detected.

4.2. *Time-resolved point/multipoint dosimetry*

With time-resolved dosimetry, the dose rate is recorded during the treatment with a given readout frequency, resulting in readout times ranging from minutes to subseconds. Such methods require detectors that can provide dose readout during treatment, such as diodes or scintillators.

Dose rate at dwell position level: Verification of the dose and dose rate is the most basic level of feedback available from time-resolved IVD. Acquisition with a subsecond rate enables measurement of the dose rate for each dwell position [26]. Hence, a direct comparison of the expected and measured dose rate can be made at the dwell position level.

Dwell time measurement: IVD with a subsecond readout rate also enables determination of the dwell time for each dwell position [27–29]. If the readout rate of the IVD system is fast enough, the timing of source movements can be determined with a precision of under 0.1 s [26,28–31]. Examples of dwell time studies can be found in Table 1.

Source tracking: Source tracking exploits measurements (e.g. dose rate) to assess the source position and can be divided into 3 categories, which are described below and illustrated in Fig. 2.

***Point detector*:** The measured dose rate by a point detector can be transformed into a distance between source and detector by using TG43 [32,33]. By adding the information from dose rate measurements at multiple positions, triangulation can be used to determine the actual position of the source or source catheter relative to the detector(s) [26,34–36].

***Flat panel detector*:** The panel is placed close to the patient (e.g. in the treatment couch underneath the patient) so that it detects photons leaving the patient's body. The panel response can be approximated by mathematical functions used to define the dwell positions [28,29,37]. Panels are available with up to ≈0.1 mm spatial resolution and acquisition rates of more than 100 frames per second (fps). However, high acquisition rates usually limit the detection area and/or require pixel binning (combination of the response of adjacent pixels). An advantage of flat panel detectors is that they can be used for commissioning of brachytherapy applicators [38] and for imaging of the patient anatomy, which enables measurements relative to the anatomy [37,39].

Slit cameras: A collimator is placed in front of a radiation detector. The collimator consists of a high-density plate, normally made of tungsten, with small holes at a fixed distance from each other. The radiation passes through the apertures and generates spots on high-resolution detectors. These can be pixelated Si-detectors [40] or charge-coupled device cameras [31].

Point detectors and some types of slit cameras provide information on source positioning relative to the detectors, not to the patient anatomy. A specific slit camera solution has demonstrated integration of the detector with an ultrasound probe; with this system, source tracking can be related to imaging and patient anatomy [40]. Likewise, flat panel detectors can be used for source tracking and can also provide anatomical information.

3D dose reconstruction: Brachytherapy dose distributions can be determined by knowing all source positions and dwell times. Dose reconstruction does not necessarily require an anatomical reference and can be calculated by following the TG43 homogeneous water approach. However, a reconstruction of the dose distribution onto the patient's anatomy is more clinically relevant than purely geometrical information, since positional offsets of some dwell positions have more impact on the dose to the tumor and organs at risk than others. With 3D dose reconstruction, uncertainties in tracked source positions are propagated into uncertainties in dose reconstruction. In addition, the 3D dose distribution depends on the used dose calculation algorithm and its own uncertainty.

DVH calculation: A 3D dose distribution may be visually difficult to

Table 1
Short summary of the information provided from phantom measurements using time-resolved methods published since 2001. Papers were sorted by the publication year.

Year Authors [citation]	Detector	Geometry	Level of source tracking	Spatial resolution	Timing resolution	Additional info
2001 Duan et al. [81]	Film-pinhole camera	Polystyrene phantom	x, y, z for each dwell position	Dwell separations of 1 mm can be distinguished	None	Post treatment analysis
2005 Nakano et al. [82]	One diamond detector on the skin	Anthropomorphic phantom	x, y, z for each dwell	2.5 mm or 2%	None	Twelve measurements were performed with a single detector at 12 positions to simulate 12 detectors
2010 Batic et al. [83]	Two pinhole detectors, 2 Si-pads for each pinhole	Air phantom with 2 needles	x, y, z for each dwell	4.6 mm absolute, 2.8 mm relative	None	Focus on relative position between 2 positions inside a catheter
2013 Smith et al. [28]	Flat panel	Solid water phantom	x, y, z for each dwell	<1.0 mm in the plane and 2.0 mm for the distance to the source	0.1 s	Focus on a 4D measurement system and characterization of an EPID panel
2013 Therriault-Proulx et al. [34]	Three plastic scintillators on a single fiber	Water phantom	z position only (along the catheter)	0.3 mm	3.0 s	The integration time was defined as a good trade-off between precision and temporal resolution
2013 Espinoza et al. [30]	11 × 11 Si diodes	Magic phantom: 3 × 30 × 30 cm solid water	x, y, z for each dwell	<0.5 mm for 75% of the positions	0.001 s	They focus on a 4D measurement system that can also measure transit time
2014 Kertzscher et al. [59]	Inorganic scintillators (Al_2O_3:C)	Simulation	Dosimeter position (x,y,z)	<0.8 mm	1.0 s	The aim is to continuously update the position of the detector throughout a treatment based on the measured dose rates
2014 Wang et al. [35]	Two inorganic scintillators (GaN)	PMMA cylinder phantom	x-position only (along the catheter)	<1.0 mm	0.1 s	The study aimed to find a method for pretreatment Q
2015 Safavi-Naeini et al. [40]	BrachyView prototype. Two 14 × 14-mm TimePix detectors in a specially designed probe with 6 cone pinholes	Plastic water	x, y, z for each dwell	<1.0 mm	None	Authors mention that they are developing a 4-detector system integrated with an ultrasound probe. The detector can acquire up to 400 fps, but dwell times larger than 0.5 s are preferable to reduce noise
2016 Guiral et al. [26]	Four inorganic scintillators (GaN)	Plastic cylinder for QA and water phantom for probe	z for each dwell	<1.0 mm	0.1 s	There were 2 systems: an expanded version of the QA phantom from Ref. [9] and a specially designed applicator
2017 Fonseca et al. [38]	Flat panel	PMMA plate	x, y, and interdwell distance for each dwell	0.2 mm	0.1 s	Technique for commissioning of applicators using source tracking
2017 Fonseca et al. [29]	Flat panel	Water phantom	x, y, z for each dwell	0.2 mm for x and y. 0.6 mm for z	0.1 s	Technique for pretreatment verification
2018 Watanabe et al. [31]	Pinhole camera with 2 holes; a scintillator plate and a CCD camera	Water phantom	x, y, z for each dwell	0.7 mm	2.0 s	The pixel intensity is directly proportional to the dwell time and could allow measurements with higher resolution than the shutter speed

Abbreviations: CCD, charge-coupled device; PMMA, poly(methyl methacrylate); QA, quality assurance.

interpret, whereas DVH metrics are considered more relevant for clinical use. DVHs can be calculated by using the reconstructed 3D dose distribution. A limitation in estimating DVHs from source tracking is that the patient anatomy may change between imaging and treatment delivery. Table 1 shows an overview of phantom studies reported in the literature since 2001. Several of the phantom studies showed submillimeter accuracy for determination of source position and sub-second accuracy for determination of dwell time for a range of phantoms and detectors.

4.3. Clinical studies

The clinical acceptance of IVD is currently limited by the laboriousness of the methods and the absence of commercial systems with high sensitivity towards clinically relevant deviations from the treatment plan.

Table 2 provides an overview of the reported clinical studies of IVD for brachytherapy. Most (20/27) of the studies reported on integrated dose from point detectors (e.g., thermoluminescent dosimeters [41–45], metal-oxide semiconductor field-effect transistors (MOSFETs) [46–48], optically stimulated luminescence detectors [49], diodes [50–52], glass detectors [53], plastic scintillators [54], and alanine dosimeters [52,55]) for different treatment sites. These studies reported maximum deviation between measured and planned dose ranging from a few percent to more than 100%. Deviations were often attributed to detector positioning uncertainties that depend on the experience of the user, verification methods, proper fixation and possible anatomical changes during the treatment. Catheter and needle reconstruction were also identified as a potential source of clinically relevant deviations [56]. One study reported that improvements in the workflow and imaging immediately prior to treatment delivery reduced maximum dose deviation from 67% to 9% [54]; indeed, deviations between measured and planned dose generally increase as the time between imaging and treatment delivery increases [47].

The likelihood of detecting errors increases significantly when time-resolved methods are used. Andersen et al. [24] concluded that the likelihood of detecting swapped catheters increased by a factor of 10 or more when time-resolved methods were used. Time-resolved methods have also been used for source tracking and dwell time measurements. In 2006, Tanderup et al. [57] evaluated the spatial stability of the applicator in relation to the IVD diode array during pulsed dose rate brachytherapy treatments. Despite promising results with phantoms (Table 1), clinical trials using source tracking are still limited. Johansen et al. [36] used a radioluminescence crystal to measure the dose rate for individual dwell positions during HDR prostate treatment. Source

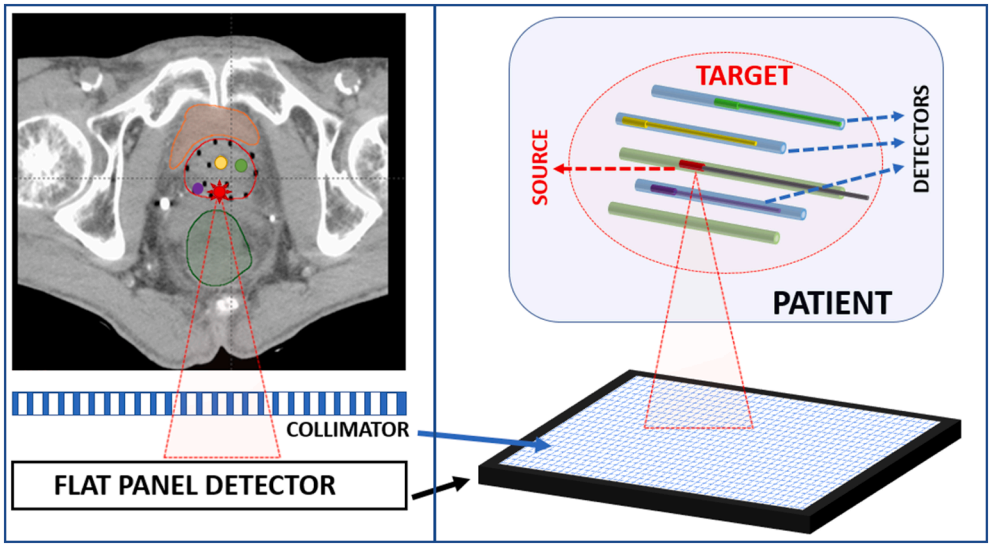

Fig. 2. Illustration of IVD performed with three different methods. a) Computed tomography image of a patient undergoing treatment for prostate cancer highlighting the bladder (orange), rectum (green), and target (red contour). The radioactive source is indicated in red. b) 3D sketch of (a). In the first method, the three circles (yellow, green, and purple) represent the catheters used for detector placement. Source tracking using point detectors is performed with the detector(s) inside or attached to the patient's body. In the second method, a flat panel detector is placed outside the patient, where it captures photons emitted by the source. In the third method, a collimator is placed on top of the imaging panel so that it works as a slit camera. Note that measurements with point detectors can be performed using one or several detectors. Although this example shows an imaging panel/slit camera placed outside the patient, there are efforts to combine this technology with ultrasound imaging probes that would be placed inside the patient [40]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

tracking in relation to the detector was based on dose rate measurements, and needle shifts were determined (mean radial needle shift of 0.2 ± 1.1 mm (1SD) and longitudinal needle shift of -0.3 ± 2.0 mm (1SD)). Smith et al. [37] used a flat panel detector for 2D source tracking for two prostate cancer patients and found a mean deviation of 1.9 mm.

5. Requirements and future directions for research, development, and clinical practice

Despite great advances in IVD, several obstacles remain to be overcome before it can become an integrated part of modern clinical brachytherapy. This section gives an overview of some minimal requirements to improve the use of IVD, including visual feedback, detection accuracy and precision, integration with treatment delivery equipment, and staffing levels.

The causes of deviations between the treatment plan and IVD measurements can be separated into four categories: 1) Deviations between delivery and treatment plan (e.g., positional offset of the source, incorrect source activity, anatomical changes); 2) Detector uncertainty (e.g., noise, calibration, energy dependence, and reproducibility); 3) Uncertainty in the position of the detector; 4) Uncertainty in the post-processing of measurements

Since the goal of IVD is to identify deviations between delivery and treatment plan, item 1 should be the dominant contributor to deviations between measured and treatment plan. Item 2 is related to the type of detector used, and item 3 is related to the clinical setup in terms of the positioning of the detector in relation to the patient anatomy. The last item is related to data post-processing. Thus, items 2 and 4 are quantities that can be determined in a controlled environment, for instance by using phantoms. It is important to keep items 2, 3 and 4 separated when reporting the uncertainties of a detector system [24,58].

5.1. Estimates of required uncertainty limits

This section will discuss the maximum detector uncertainty a system can have to be clinically relevant. The analysis is based on Gaussian uncertainty distributions for detection. Five parameters are important for the analysis.

***Source tracking uncertainty*:** The uncertainty (1SD) of the detector system including post-processing (Section 5, items 2 and 4).
***Clinical threshold*:** A threshold level for a deviation to be considered of clinical relevance. For instance, if a 5 mm or 10 mm deviation in a source position is considered important for the quality of the treatment, these would be used as the clinical thresholds.
***Action level*:** The action level is the threshold at which an alarm should be set to indicate when a given deviation exceeds the threshold. Ideally, the action level should be equal to the clinical threshold, but the uncertainty from the detector might require a different action level, as will be described below.
***Sensitivity*:** The sensitivity is defined as the fraction of detected events occurring beyond a given clinical threshold. For example, if the clinical threshold is 10 mm and the system can identify 90% of 10 mm deviations, the sensitivity is 90%.
***False alarms*:** A false alarm is a measurement that is beyond the action level but for which the clinical threshold has not been reached. For example, 2 mm offsets are frequent deviations between delivery and treatment plan, but offsets of this magnitude normally have minor clinical impact. If, for instance, 10% of the 2 mm deviations trigger an alarm, the incidence of false alarms at 2 mm is 10%.

It is beyond the scope of this report to provide specific clinical thresholds or action levels or acceptable levels of sensitivity and false alarms since. Rather, our aim is to discuss the influence of IVD system uncertainties on the ability to detect relevant deviations between delivery and treatment plan. Deviations in dose and DVH metrics are clinically more relevant than dwell position deviations. However, 3D dose and DVH calculations, based on source tracking, have not been implemented yet. Therefore, a clinically relevant threshold based on dose deviations would be hard to achieve using source tracking whilst a threshold based on dwell position deviations is more realistic. Typical clinical uncertainties are presented in the study of Kirisits et al [58]. The methodology to calculate and express uncertainty should follow international standards [23].

Fig. 3 shows the incidence of alarms at different magnitudes of source position offsets and action levels. Estimates of the incidence of alarms is provided for three different true offsets and for four different

Table 2
Short summary of the information provided from clinical brachytherapy trials published between 2017 and 2020 (see Supplementary material B for publications between 1999 and 2020). For brevity's sake, only treatment site (GYN = gynecological; PR = prostate; BR = breast; TH = thorax; HN = head and neck; SK = Skin; NPC = nasopharyngeal carcinoma), number of treatments (including multiple fractions for the same patient), detector, maximum deviation (MD), and main conclusions are reported. Accuracy and uncertainties reported in this table use the metrics reported by the authors for each study and may differ among them. Papers were sorted by the publication year. *Studies that used source tracking and/or time-resolved methods.

Year	Site	Detector	No. Treated	MD	Additional info
2017 Wagner et al. [55]	PR	Alanine/ ESR	15	≈100.0%	Alanine strands were inserted into a Foley catheter. Needles and detector positions were measured using ultrasound images. The detector volume could not be clearly defined in some of the cases. Reported uncertainty 5.0%
2017 Carrara et al. [47]	GYN	MOSkin	26	<14.0%	Dosimeters placed on top of the rectal probe. Large differences (>36.0%) were traced to a longitudinal probe displacement and not included in the analysis. Deviation between planned and measured doses increased with increasing time between imaging and treatment. Reported uncertainty 6.2% (k = 1 – MOSkin) and 7.1% (k = 1 – TPS).
2017 Jaselske et al. [41]	HN, BR	TLD	>6	≈22.0%	Dosimeters inserted into catheters/needles. Reported an increased difference in every subsequent fraction. Reported uncertainty 17.9%.
2017 Van Gellekom et al. [84]	GYN	MOSFET	50	>14.0%	Dosimeters inserted into a Fletcher or MUPIT applicator. Additional imaging should be performed for measured differences larger than 10.0%. Overall reported uncertainty 9.0% (k = 2).
2018 Smith et al. [37]	*PR	Flat panel	2	4.9 mm	EPID positioned under the patient couch used for imaging (additional X-ray source) and source tracking in 2D. Reported uncertainty 2.2 mm
2018 Johansen et al. [36]	*PR	Opt. fiber (Al_2O_3:C)	20	≈ 16.9%	Dosimeters inserted into catheters/needles. Time-resolved measurements. MR scans acquired just before and after the treatment. Reported uncertainty 5.0% (k = 1)
2018 Melchert et al. [46]	BR, TH, HN	MOSFET	12	≈ 56.0%	Dosimeters inserted into catheters/needles. A long interval between needle implantation and imaging can reduce positioning uncertainties due to edema. Reported uncertainty 4.0% (detector response) ± 1 mm positioning.
2018 Belley et al. [85]	*GYN	Opt. fiber/ TLD	30	< 20.0%	Dosimeters at the surface of a vaginal cylinder. Real-time dose rate monitoring. Reported uncertainty 13.9% (k = 2).
2019 Jamalludin et al. [86]	SK	MOSkin	5	24.0% (target) 32.0% (OAR)	MOSkin was placed between the arm and the chest of the patient (HDR Cobalt-60). The tumor was located at the medial aspect of the right arm. Differences were attributed to backscattering from lead shielding and TPS inaccuracies near the patient surface (TG43-based dose calculation). Reported uncertainty 8.4% (k = 1).
2020 Jamalludin et al. [87]	GYN	MOSkin/ diode	48	greater than 37.0%	MOSkin attached to diode during 18 sessions (HDR Cobalt-60). Doses measured with MOSkin were higher than planned for 44.0% of the cases, while doses measured with diodes were lower than planned for all the treatments. Reported uncertainty 5.2% (k = 1) and 6.6% (k = 1) for the detector and TPS, respectively.

Abbreviations: HDR, high dose rate; OAR, organ at risk; TPS, treatment planning system; TLD, thermoluminescent dosimeter; MOSFET, metal–oxide semiconductor field-effect transistor; MR, magnetic resonance; MUPIT, Martinez universal perineal interstitial template; ESR, electron spin resonance; OSLD, optically stimulated luminescent dosimeter; ICRU, International Commission on Radiation Units and Measurements; RPLGD, radio-photoluminescence glass dosimeter.

source tracking uncertainties. Selected examples of the percentage of alarms for a given source tracking uncertainty and action level based on the three true offsets are shown in the Supplementary material C. A source tracking uncertainty of 1 mm or 2 mm (1SD) allows for excellent sensitivity at detecting 10 mm deviations, for a low incidence of false alarms. If the source tracking uncertainty is 3 mm (1SD) or lower, it is difficult to choose an action level that is sensitive to detecting 10 mm deviations without causing a high incidence of false alarms. A large detector uncertainty, therefore, might limit the usage of IVD to gross errors.

5.1.1. Point detector system uncertainty for source tracking

This section gives an estimate of the requirements for detector uncertainty in cases where the dose rate is used as a direct measure or indirectly for source tracking. Under the approximation that the dose rate ($\dot{D}$) is inversely dependent on the square of the distance (r^2) between the source and the detector it is possible to translate thresholds for geometrical deviation investigated above into requirements for dosimetric deviation through the following relationship (for a point detector):

$$\frac{\Delta\dot{D}}{\dot{D}} = \frac{-2\Delta r}{r} \quad (1)$$

where $\Delta\dot{D}/\dot{D}$ is the relative dosimetric deviation and Δr the geometric deviation [36].

Fig. 4 shows source tracking uncertainty for point detectors as a function of r for different levels of dose rate deviation (based on the estimate given in Eq. (1)). Deviation in dose measurement of 5% and 10% result in deviation in the geometric prediction (Δr) of 0.25 mm and 0.5 mm at a 10 mm distance (r), and of 1.25 mm and 2.5 mm at a 50 mm distance (r), respectively. It should be noted that these estimates are based on a single point detector and a single source position. If several point detectors or several source positions are used for source tracking, the accuracy will be improved by the larger amount of data.

5.1.2. Position of the detector for source tracking

A major contribution to deviations in the measured dose rate may be offsets in the detector position. Some algorithms correct for shifts in detector position by continuously updating the most probable detector position on the basis of the already-measured dwell positions [59]. The positional uncertainty of the detector can be divided into two parts:

Determination of the detector position: It is essential to know the detector position in relation to both the anatomy and the brachytherapy implant. For internally placed detectors, the limiting factor is the visibility of the detector on the images used for identification of the detector. For externally placed detectors like flat panels and slit cameras, it

is important to place the patient with high precision relative to the detector, or to directly relate the detector to the patient and implant through anatomical imaging [25,37,60].

Stability of the detector position: During treatment, it is important that the detector is not displaced. Proper fixation is needed, but even with proper fixation, displacements can occur due to anatomical changes in case of internal detectors [32]. For external detectors, the problem stems from movement of the patient in relation to the detector.

5.1.3. Dwell time measurements

Some clinics do not accept treatment plan dwell times shorter than 0.5 s due to the time it takes for the source to move between dwell positions (transit time) [61,62]. In addition, in modern afterloaders, the minimum dwell time depends on the distance between dwell positions [63]. The aim of measuring time is to ensure that the dwell times are correct. Johansen et al. [27] estimated that a precision of at least 0.2 s is sufficient to identify timing deviations with clinical impact.

5.1.4. Accuracy of current detector systems

The accuracy of current state-of-the-art detectors is shown in Supplementary material D to illustrate the level of accuracy that can be obtained today and the importance of reporting the various contributions to the uncertainties. The table shows that with recent detector developments, the limiting factor is the positioning of the detector.

5.2. Software and hardware integration

This section provides a list of requirements needed to establish suitable communication between IVD systems, the afterloader delivery equipment, and the treatment planning system (TPS). The additions would provide basic functions that are currently lacking and should ideally be vendor agnostic.

5.2.1. Integration with the brachytherapy afterloader

Currently, IVD systems use measurements to infer which position the afterloader is treating. It would be a significant step forward if the afterloader could communicate to the IVD system which source position it is intended to be treating. Ideally, this integration could also allow automatic treatment interruption, if a measured deviation reaches a certain action level, hence improving patient safety.

5.2.2. Integration with the TPS

The following is a list of possible features to be added to TPSs. The first four items listed below could be considered minimal requirements, as they do not require the development of new techniques. More advanced features, such as outcome prediction (tumor control probability/normal tissue complication probability [TCP/NTCP] models) and treatment plan adaptation, require further developments.

Export of dwell positions and times: The TPS should export the source dwell positions and times. This could include fiducial markers for

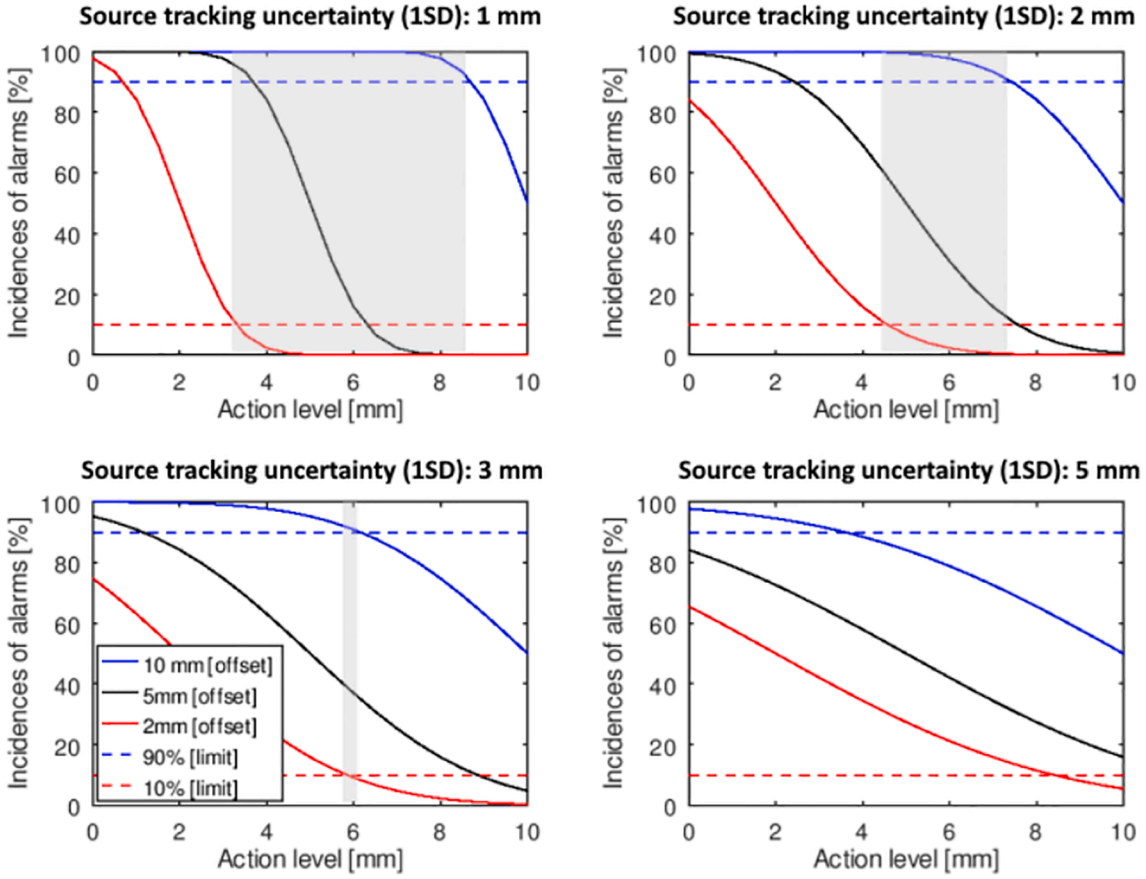

Fig. 3. Estimate of the fraction of events identified as being above a given action level for four different source tracking uncertainty levels (incidence of alarms). The incidence of alarms is shown for 3 true positional offsets: 10 mm (blue), 5 mm (black), and 2 mm (red). The dashed lines represent the 10% and 90% incidence levels as examples of acceptable levels of false alarms and deviation sensitivity, respectively. The shaded area represents the area in which false alarms for 2 mm offsets are below 10% and the sensitivity at catching 10 mm deviations is more than 90%. Source tracking uncertainties of 3 mm or less allow for reliable detection of 10 mm deviations, while 1 mm uncertainty is needed for reliable detection of 5 mm deviations. If a detector system has a detection accuracy of 5 mm (1SD), a sensitivity of 80% requires an action level of 6 mm, which causes almost every fifth offset at 2 mm to trigger a false alarm. Furthermore, a substantial number of correctly placed source positions (offset = 0 mm) will also lead to alarms. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

potential registration. In general, TPSs already have this capability. However, dwell time corrections (e.g. rescaling due to air-kerma strength, transit time and minimum dwell time) [61,63] are applied just before the treatment by the treatment console. Therefore, measurements should be compared to the plan executed by the afterloader and this information should be accessible.

Export of dose rate at a single point: To support dose rate measurements (as a function of treatment delivery), the TPS should export the expected dose rate at points defined by the user.

Reconstruction of dose and DVH from measured dwell positions and times: The TPS should import measured dwell times and positions from the IVD system and calculate dose distributions and DVH metrics.

Tools for evaluation: The TPS should provide tools for comparison of a specified plane or the entire dose volume (absolute difference, 2D/3D gamma, etc.), TCP/NTCP models to estimate the clinical effect of a dose deviation, and tools to pinpoint the its most likely cause. Such tools could employ artificial intelligence as already evaluated for treatment planning optimization [64] and inter-fraction adaptation [65].

Measured dose accumulation and treatment plan adaptation: The dose differences reported by an IVD system may be used for inter-fraction adaptation.

Consolidation of the treatment control system and TPS: Many of the features required by a brachytherapy verification system dissolve the distinct line between a planning system and a treatment delivery control system. A comprehensive brachytherapy system similar to systems commonly used in external beam radiotherapy would consider patient anatomy and position at the time of treatment and the previously delivered dose. It would also provide online adaptive planning, treatment delivery verification, and dose summation.

5.3. Resources and staffing

An important factor affecting the widespread usage of IVD is the resources required to acquire, commission, and run the systems. Brachytherapy requires relatively inexpensive equipment (compared to external beam radiotherapy). At the same time, brachytherapy is time consuming and requires many manual procedures. Adding steps to an already busy schedule would have a negative effect on the adoption of IVD. Two surveys performed by GEC-ESTRO [66,67] estimated that an IVD system should not add more than 1 h of additional work to a treatment. This additional workload can be divided into two categories:

Commissioning, quality assurance and pre-treatment verification: This step ensures accurate measurements. It would not add to the timing of the brachytherapy procedure, as it can be performed prior to treatment. In addition, IVD audits in analogy to dosimetry audits [68–70] performed by an external organization could provide relevant information on accuracy and a comparison between different centers. Audits of IVD systems would require dedicated phantoms and protocols to mimic relevant clinical scenarios.

IVD: This involves the procedures performed while the patient is present: positioning of the detector, possible calculation of the expected dose pattern, and initiation of IVD measurements. Ideally, this would be fully automated.

6. Discussion

In addition to IVD, other techniques for treatment verification in brachytherapy are continually developing. These methods can be complementary to or combined with IVD, so we will briefly describe two techniques that have received much attention in the last decade. Both techniques are related to tracking, which again emphasizes the focus on identifying possible positional offsets of the source.

6.1. Imaging

Imaging is already a key part of treatment planning for brachytherapy. As in external beam radiotherapy, the field is converging towards online monitoring using images (in-room imaging). Nose et al. [71] used a C-arm to perform X-ray imaging during treatment. By increasing the intensity of the X-rays and reducing the number of frames per second (fps), they were able to make images of the source together with the anatomy of the patient. Despite the reduction in fps, X-ray images still lead to additional radiation exposure.

Furthermore, a prototype system combining MR imaging (MRI) and an afterloader has been reported [72]. The advantage of MRI-guided therapy in brachytherapy compared to external beam radiotherapy is that a fully integrated system like the MR-linac is not necessary for brachytherapy. However, because most MRI scanners are not located in rooms that are appropriately shielded for brachytherapy, adopting this system would require infrastructural changes.

The clear advantage of imaging is the ability to relate the source position to the anatomy. Imaging and IVD can also be combined to relate the detector position to the anatomy, as described by Smith et al. [37], before or during the treatment. Image acquisition and registration (e.g. with the planning CT) will add additional uncertainties components that should be evaluated.

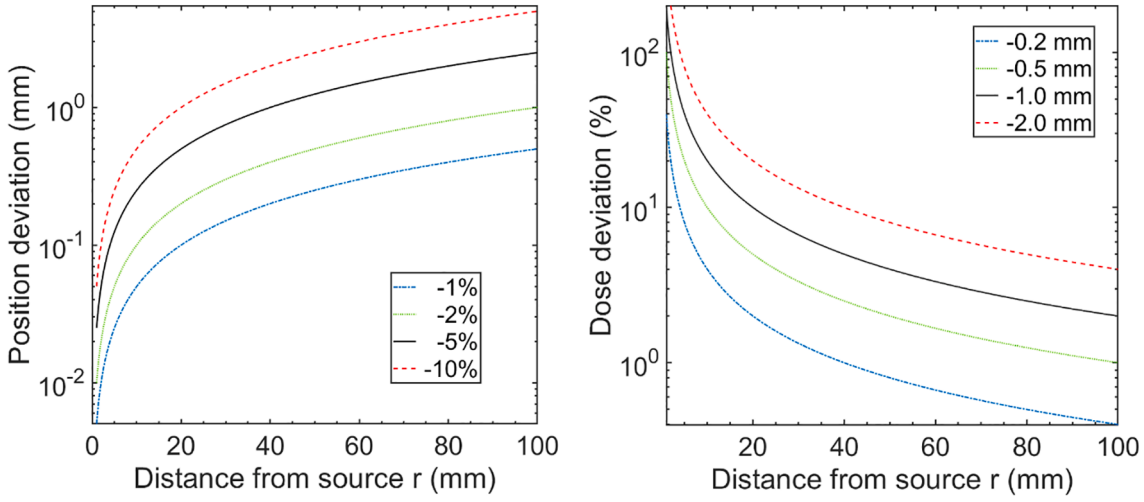

Fig. 4. Position and dose deviation as a function distance between the source and the detector (r). a) Deviation in the geometric prediction for different levels of dose deviations (−1%, −2%, −5%, and −10%). b) Relative dose deviation for four different positional deviations as a function of r. This does not apply to flat panel detectors if mathematical fits are applied to define the source position.

6.2. Electromagnetic tracking

Electromagnetic tracking (EMT) is another way of performing tracking. A small sensor in the form of a coil is tracked using an EM field generator. The coil can be tracked relative to the generator with a precision of under 0.2 mm [73]. However, this is not a direct tracking of the source. Another possibility would be to add the coil to the tip of the source cable. This would enable direct tracking of the source.

EMT could also be combined with IVD. One major issue in efforts to implement IVD at the moment is the uncertainty associated with the positioning of the detector (Section 4.2.2). A first attempt to solve this problem was demonstrated with the RADPOS system, in which an EMT device was coupled to a MOSFET detector [74]. Unfortunately, the EMT technology implemented did not allow for position-reading accuracy of better than 1 mm. More recently, a different EMT technology was used by Tho and Beaulieu [73]. This detector's accuracy was on the order of 0.2–0.3 mm between 5 and 30 cm from the center of the EM field generator, which corresponds to the relevant region for clinical use [75]. This level of accuracy allows for dose measurement uncertainty of 5% for a detector at 10 mm from the source and better at larger distances. Furthermore, knowing the detector position in real time enables its use as input when implementing the source tracking approach [76,77].

6.3. Perspectives for clinical use of IVD

The focus of this report has been the requirements for future developments of IVD systems, both from an R&D point of view and for commercialization. It is, however, worth noting that despite the ongoing need for further development of IVD, several systems for real-time IVD are currently on the verge of clinical usage. We will therefore end this report by looking at the future clinical uses of IVD and how improvements could improve the clinical standards of brachytherapy.

Clinical studies: Most of the novel and advanced IVD systems have only been tested in laboratories with phantom measurements. Very few reports of clinical studies are available, and they are limited to proof-of-concept studies with small numbers of patients and treatment sites. The next step should be to test more systems in clinical studies with larger cohorts of patients to establish the clinical value of advanced IVD. The clinical environment is very different from a fixed phantom. Furthermore, feedback from users is essential. Finally, clinical studies will help raise the awareness of the need for IVD.

Reporting of errors: A major concern in brachytherapy is a lack of knowledge regarding the frequency and nature of errors. It is therefore important that once routine clinical use of IVD is initiated, errors as well as near-misses are reported. The UK and France have initiatives to collect data on errors and near-misses in radiotherapy for educational purposes [78,79]. The European Radiological Protection Act 1991 (Ionizing Radiation) Regulations 2019 establishes that each Member State should have mechanisms to register errors and near-misses ensuring timely dissemination of lessons learned from significant medical exposure events [80]. Such registries can greatly benefit the brachytherapy community and would provide useful information for future developments in brachytherapy.

Future efforts in the development of IVD systems would greatly benefit from integration with afterloaders and TPSs, both to provide the necessary treatment information for reference and for the evaluation of the measurements. The next steps towards clinical implementation will require large clinical trials and systematic reporting of errors and near-misses. It is of the utmost importance that the sensitivity to different types of errors is well understood for each IVD system so that end-users can select the most suitable method for their needs. Furthermore, departmental policies may vary; some departments may focus on avoiding gross errors with major clinical impact, while others may seek to improve the treatment by avoiding errors that have more limited clinical impact. Whatever methods are adopted, IVD would also benefit from in-room imaging to correlate measurements and patient anatomy and reduce measurement uncertainties. The clinical use of IVD solutions will affect workflows and require additional staffing to use the systems and investigate alarms. This issue can be mitigated by integrating automated evaluation systems, efficiently placing detectors, and setting appropriate action levels. The potential benefit will justify the use of IVD once accurate methods are commercially available. In addition, IVD could become mandatory to satisfy increasing medico-legal requirements to record the dose delivered to patients.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: G. Paiva Fonseca and F. Verhaegen declares research collaborations with Varian Medical Systems.

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Appendix A. Supplementary data

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References

[1] Shaaer A, Davidson M, Semple M, Nicolae A, Mendez LC, Chung H, et al. Clinical evaluation of an MRI-to-ultrasound deformable image registration algorithm for prostate brachytherapy. Brachytherapy 2019;18:95–102. https://doi.org/10.1016/j.brachy.2018.08.006.
[2] Aristei C, Lancellotta V, Piergentini M, Costantini G, Saldi S, Chierchini S, et al. Individualized 3D-printed templates for high-dose-rate interstitial multicathether brachytherapy in patients with breast cancer. Brachytherapy 2018;18:57–62. https://doi.org/10.1016/j.brachy.2018.09.007.
[3] Han DY, Safigholi H, Soliman A, Ravi A, Leung E, Scanderbeg DJ, et al. Direction modulated brachytherapy for treatment of cervical cancer. II: Comparative planning study with intracavitary and intracavitary-interstitial techniques. Int J Radiat Oncol Biol Phys 2016;96:440–8. https://doi.org/10.1016/j.ijrobp.2016.06.015.
[4] Ma Y, Vijande J, Ballester F, Tedgren AC, Granero D, Haworth A, et al. A generic TG-186 shielded applicator for commissioning model-based dose calculation algorithms for high-dose-rate (192) Ir brachytherapy. Med Phys 2017;44:5961–76. https://doi.org/10.1002/mp.12459.
[5] Beaulieu L, Carlsson Tedgren A, Carrier JF, Davis SD, Mourtada F, Rivard MJ, et al. Report of the Task Group 186 on model-based dose calculation methods in brachytherapy beyond the TG-43 formalism: current status and recommendations for clinical implementation. Med Phys 2012;39:6208–36. https://doi.org/10.1118/1.4747264.
[6] Papagiannis P, Pantelis E, Karaiskos P. Current state of the art brachytherapy treatment planning dosimetry algorithms. Br J Radiol 2014;87:20140163. https://doi.org/10.1259/bjr.20140163.
[7] Sturdza A, Potter R, Fokdal LU, Haie-Meder C, Tan LT, Mazeron R, et al. Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study. Radiother Oncol 2016;120:428–33. https://doi.org/10.1016/j.radonc.2016.03.011.
[8] Astrom L, Grusell E, Sandin F, Turesson I, Holmberg L. Two decades of high dose rate brachytherapy with external beam radiotherapy for prostate cancer. Radiother Oncol 2018;127:81–7. https://doi.org/10.1016/j.radonc.2017.12.025.
[9] Valentin J. Prevention of high-dose-rate brachytherapy accidents. ICRP Publication 97. Ann ICRP 2005;35(1–51). https://doi.org/10.1016/j.icrp.2005.05.002.
[10] Honderden vrouwen onjuist bestraald in Maastricht. 2014 [cited 2018 13/11/2018]; Available from: https://www.rtlnieuws.nl/node/1807366.
[11] Radiation equipment may not have correctly targeted cervical cancer in 25 patients. 2019 04/06/2019]; Available from: https://www.cbc.ca/news/canada/hamilton/radiation-equipment-juravinski-cancer-centre-1.4964780.
[12] Tanderup K, Beddar S, Andersen CE, Kertzscher G, Cygler JE. In vivo dosimetry in brachytherapy. Med Phys 2013;40:070902. https://doi.org/10.1118/1.4810943.
[13] Huq MS, Fraass BA, Dunscombe PB, Gibbons Jr JP, Ibbott GS, Mundt AJ, et al. The report of Task Group 100 of the AAPM: Application of risk analysis methods to radiation therapy quality management. Med Phys 2016;43:4209. https://doi.org/10.1118/1.4947547.

[14] Schmid MP, Kirisits C, Nesvacil N, Dimopoulos JCA, Berger D, Pötter R. Local recurrences in cervical cancer patients in the setting of image-guided brachytherapy: A comparison of spatial dose distribution within a matched-pair analysis. Radiother Oncol 2011;100:468–72. https://doi.org/10.1016/j.radonc.2011.08.014.
[15] Hoskin PJ, Rojas AM, Ostler PJ, Hughes R, Bryant L, Lowe GJ. Dosimetric predictors of biochemical control of prostate cancer in patients randomised to external beam radiotherapy with a boost of high dose rate brachytherapy. Radiother Oncol 2014;110:110–3. https://doi.org/10.1016/j.radonc.2013.08.043.
[16] Tanderup K, Hellebust TP, Lang S, Granfeldt J, Potter R, Lindegaard JC, et al. Consequences of random and systematic reconstruction uncertainties in 3D image based brachytherapy in cervical cancer. Radiother Oncol 2008;89:156–63. https://doi.org/10.1016/j.radonc.2008.06.010.
[17] Uzan J, Nahum AE, Syndikus I. Prostate dose-painting radiotherapy and radiobiological guided optimisation enhances the therapeutic ratio. Clin Oncol (R Coll Radiol) 2016;28:165–70. https://doi.org/10.1016/j.clon.2015.09.006.
[18] Pasalic D, Kuban DA, Allen PK, Tang C, Mesko SM, Grant SR, et al. Dose escalation for prostate adenocarcinoma: a long-term update on the outcomes of a phase 3, single institution randomized clinical trial. Int J Radiat Oncol Biol Phys 2019;104:790–7. https://doi.org/10.1016/j.ijrobp.2019.02.045.
[19] Simnor T, Li S, Lowe G, Ostler P, Bryant L, Chapman C, et al. Justification for inter-fraction correction of catheter movement in fractionated high dose-rate brachytherapy treatment of prostate cancer. Radiother Oncol 2009;93:253–8. https://doi.org/10.1016/j.radonc.2009.09.015.
[20] Poder J, Carrara M, Howie A, Cutajar D, Bucci J, Rosenfeld A. Derivation of in vivo source tracking error thresholds for TRUS-based HDR prostate brachytherapy through simulation of source positioning errors. Brachytherapy 2019;18:711–9. https://doi.org/10.1016/j.brachy.2019.05.001.
[21] Buus S, Lizondo M, Hokland S, Rylander S, Pedersen EM, Tanderup K, et al. Needle migration and dosimetric impact in high-dose-rate brachytherapy for prostate cancer evaluated by repeated MRI. Brachytherapy 2018;17:50–8. https://doi.org/10.1016/j.brachy.2017.08.005.
[22] Pantelis E, Papagiannis P, Anagnostopoulos G, Baltas D, Karaiskos P, Sandilos P, et al. Evaluation of a TG-43 compliant analytical dosimetry model in clinical 192Ir HDR brachytherapy treatment planning and assessment of the significance of source position and catheter reconstruction uncertainties. Phys Med Biol 2004;49:55–67. https://doi.org/10.1088/0031-9155/49/1/004.
[23] ISO/IEC, Uncertainty of measurement — Part 3: Guide to the expression of uncertainty in measurement (GUM:1995). 2008, JCGM.
[24] Andersen CE, Nielsen SK, Lindegaard JC, Tanderup K. Time-resolved in vivo luminescence dosimetry for online error detection in pulsed dose-rate brachytherapy. Med Phys 2009;36:5033–43. https://doi.org/10.1118/1.3238102.
[25] Carrara M, Tenconi C, Rossi G, Borroni M, Cerrotta A, Grisotto S, et al. In vivo rectal wall measurements during HDR prostate brachytherapy with MOSkin dosimeters integrated on a trans-rectal US probe: Comparison with planned and reconstructed doses. Radiother Oncol 2016;118:148–53. https://doi.org/10.1016/j.radonc.2015.12.022.
[26] Guiral P, Ribouton J, Jalade P, Wang R, Galvan JM, Lu GN, et al. Design and testing of a phantom and instrumented gynecological applicator based on GaN dosimeter for use in high dose rate brachytherapy quality assurance. Med Phys 2016;43:5240. https://doi.org/10.1118/1.4961393.
[27] Johansen JG, Kertzscher G, Jorgensen EB, Rylander S, Bentzen L, Hokland SB, et al. Dwell time verification in brachytherapy based on time resolved in vivo dosimetry. Phys Med 2019;60:156–61. https://doi.org/10.1016/j.ejmp.2019.03.031.
[28] Smith RL, Taylor ML, McDermott LN, Haworth A, Millar JL, Franich RD. Source position verification and dosimetry in HDR brachytherapy using an EPID. Med Phys 2013;40:111706. https://doi.org/10.1118/1.4823758.
[29] Fonseca GP, Podesta M, Bellezzo M, Van den Bosch MR, Lutgens L, Vanneste BGL, et al. Online pretreatment verification of high-dose rate brachytherapy using an imaging panel. Phys Med Biol 2017;62:5440–61. https://doi.org/10.1088/1361-6560/aa7028.
[30] Espinoza A, Beeksma B, Petasecca M, Fuduli I, Porumb C, Cutajar D, et al. The feasibility study and characterization of a two-dimensional diode array in "magic phantom" for high dose rate brachytherapy quality assurance. Med Phys 2013;40:111702. https://doi.org/10.1118/1.4822736.
[31] Watanabe Y, Muraishi H, Takei H, Hara H, Terazaki T, Shuto N, et al. Automated source tracking with a pinhole imaging system during high-dose-rate brachytherapy treatment. Phys Med Biol 2018;63:145002. https://doi.org/10.1088/1361-6560/aacdc9.
[32] Nath R, Anderson LL, Luxton G, Weaver KA, Williamson JF and Meigooni AS, Dosimetry of interstitial brachytherapy sources: recommendations of the AAPM Radiation Therapy Committee Task Group No. 43. American Association of Physicists in Medicine. Med Phys. 1995; 22:209-34. 10.1118/1.597458.
[33] Rivard MJ, Coursey BM, DeWerd LA, Hanson WF, Huq MS, Ibbott GS, et al., Update of AAPM Task Group No. 43 Report: A revised AAPM protocol for brachytherapy dose calculations. Med Phys. 2004; 31:633-74. 10.1118/1.1646040.
[34] Therriault-Proulx F, Beddar S, Beaulieu L. On the use of a single-fiber multipoint plastic scintillation detector for 192Ir high-dose-rate brachytherapy. Med Phys 2013;40:062101. https://doi.org/10.1118/1.4803510.
[35] Wang R, Ribouton J, Pittet P, Guiral P, Jalade P, Lu GN. Implementation of GaN based real-time source position monitoring in HDR brachytherapy. Radiat Meas 2014;71:293–6. https://doi.org/10.1016/j.radmeas.2014.05.021.
[36] Johansen JG, Rylander S, Buus S, Bentzen L, Hokland SB, Sondergaard CS, et al. Time-resolved in vivo dosimetry for source tracking in brachytherapy. Brachytherapy 2018;17:122–32. https://doi.org/10.1016/j.brachy.2017.08.009.
[37] Smith RL, Hanlon M, Panettieri V, Millar JL, Matheson B, Haworth A, et al. An integrated system for clinical treatment verification of HDR prostate brachytherapy combining source tracking with pretreatment imaging. Brachytherapy 2018;17:111–21. https://doi.org/10.1016/j.brachy.2017.08.004.
[38] Fonseca GP, Van den Bosch MR, Voncken R, Podesta M, Verhaegen F. A novel system for commissioning brachytherapy applicators: example of a ring applicator. Phys Med Biol 2017;62:8360–75. https://doi.org/10.1088/1361-6560/aa8d0a.
[39] Fonseca G, Podesta M, Reniers B, Verhaegen F. MO-AB-BRA-03: development of novel real time in vivo EPID treatment verification for brachytherapy. Med Phys 2016;43. https://doi.org/10.1118/1.4957155. 3691-3691.
[40] Safavi-Naeini M, Han Z, Alnaghy S, Cutajar D, Petasecca M, Lerch MLF, et al. BrachyView, a novel in-body imaging system for HDR prostate brachytherapy: Experimental evaluation. Med Phys 2015;42:7098–107. https://doi.org/10.1118/1.4935866.
[41] Jaselske E, Adliene D, Rudzianskas V, Urbonavicius BG, Inciura A. In vivo dose verification method in catheter based high dose rate brachytherapy. Phys Med 2017;44:1–10. https://doi.org/10.1016/j.ejmp.2017.11.003.
[42] Brezovich IA, Duan J, Pareek PN, Fiveash J, Ezekiel M. In vivo urethral dose measurements: a method to verify high dose rate prostate treatments. Med Phys 2000;27:2297–301. https://doi.org/10.1118/1.1312811.
[43] Anagnostopoulos G, Baltas D, Geretschlaeger A, Martin T, Papagiannis P, Tselis N, et al. In vivo thermoluminescence dosimetry dose verification of transperineal 192Ir high-dose-rate brachytherapy using CT-based planning for the treatment of prostate cancer. Int J Radiat Oncol Biol Phys 2003;57:1183–91.
[44] Das R, Toye W, Kron T, Williams S, Duchesne G. Thermoluminescence dosimetry for in-vivo verification of high dose rate brachytherapy for prostate cancer. Australas Phys Eng Sci Med 2007;30:178–84.
[45] Toye W, Das R, Kron T, Franich R, Johnston P, Duchesne G. An in vivo investigative protocol for HDR prostate brachytherapy using urethral and rectal thermoluminescence dosimetry. Radiother Oncol 2009;91:243–8. https://doi.org/10.1016/j.radonc.2008.08.016.
[46] Melchert C, Soror T, Kovacs G. Quality assurance during interstitial brachytherapy: in vivo dosimetry using MOSFET dosimeters. J Contemp Brachytherapy 2018;10:232–7. https://doi.org/10.5114/jcb.2018.76748.
[47] Carrara M, Romanyukha A, Tenconi C, Mazzeo D, Cerrotta A, Borroni M, et al. Clinical application of MOSkin dosimeters to rectal wall in vivo dosimetry in gynecological HDR brachytherapy. Phys Med 2017;41:5–12. https://doi.org/10.1016/j.ejmp.2017.05.003.
[48] Cygler JE, Saoudi A, Perry G. Morash C and E C, Feasibility study of using MOSFET detectors for in vivo dosimetry during permanent low-dose-rate prostate implants. Radiother Oncol 2006;80:296–301. https://doi.org/10.1016/j.radonc.2006.07.008.
[49] Sharma R, Jursinic PA. In vivo measurements for high dose rate brachytherapy with optically stimulated luminescent dosimeters. Med Phys 2013;40:071730. https://doi.org/10.1118/1.4811143.
[50] Allahverdi M, Sarkhosh M, Aghili M, Jaberi R, Adelnia A, Geraily G. Evaluation of treatment planning system of brachytherapy according to dose to the rectum delivered. Radiat Prot Dosim 2012;150:312–5. https://doi.org/10.1093/rpd/ncr415.
[51] Waldhausl C, Wambersie A, Potter R, Georg D. In-vivo dosimetry for gynaecological brachytherapy: physical and clinical considerations. Radiother Oncol 2005;77:310–7. https://doi.org/10.1016/j.radonc.2005.09.004.
[52] Alecu R, Alecu M. In-vivo rectal dose measurements with diodes to avoid misadministrations during intracavitary high dose rate brachytherapy for carcinoma of the cervix. Med Phys 1999;26:768–70. https://doi.org/10.1118/1.598598.
[53] Nose T, Koizumi M, Yoshida K, Nishiyama K, Sasaki J, Ohnishi T, et al. In vivo dosimetry of high-dose-rate brachytherapy: study on 61 head-and-neck cancer patients using radiophotoluminescence glass dosimeter. Int J Radiat Oncol Biol Phys 2005;61:945–53. https://doi.org/10.1016/j.ijrobp.2004.10.031.
[54] Suchowerska N, Jackson M, Lambert J, Yin YB, Hruby G, McKenzie DR. Clinical trials of a urethral dose measurement system in brachytherapy using scintillation detectors. Int J Radiat Oncol Biol Phys 2011;79:609–15. https://doi.org/10.1016/j.ijrobp.2010.03.030.
[55] Wagner D, Hermann M, Hille A. In vivo dosimetry with alanine/electron spin resonance dosimetry to evaluate the urethra dose during high-dose-rate brachytherapy. Brachytherapy 2017;16:815–21. https://doi.org/10.1016/j.brachy.2017.04.003.
[56] Mason J, Mamo A, Al-Qaisieh B, Henry AM, Bownes P. Real-time in vivo dosimetry in high dose rate prostate brachytherapy. Radiother Oncol 2016;120:333–8. https://doi.org/10.1016/j.radonc.2016.05.008.
[57] Tanderup K, Christensen JJ, Granfeldt J, Lindegaard JC. Geometric stability of intracavitary pulsed dose rate brachytherapy monitored by in vivo rectal dosimetry. Radiother Oncol 2006;79:87–93. https://doi.org/10.1016/j.radonc.2006.02.016.
[58] Kirisits C, Rivard MJ, Baltas D, Ballester F, De Brabandere M, van der Laarse R, et al. Review of clinical brachytherapy uncertainties: analysis guidelines of GEC-ESTRO and the AAPM. Radiother Oncol 2014;110:199–212. https://doi.org/10.1016/j.radonc.2013.11.002.
[59] Kertzscher G, Andersen CE, Tanderup K. Adaptive error detection for HDR/PDR brachytherapy: guidance for decision making during real-time in vivo point dosimetry. Med Phys 2014;41:052102. https://doi.org/10.1118/1.4870438.
[60] Verhaegen F, Palefsky S, Rempel D, Poon E. Imaging with Iridium photons: an application in brachytherapy. Med Imaging 2007;6510. https://doi.org/10.1117/12.707983.

[61] Fonseca GP, Landry G, Reniers B, Hoffmann A, Rubo RA, Antunes PC, et al. The contribution from transit dose for (192)Ir HDR brachytherapy treatments. Phys Med Biol 2014;59:1831–44. https://doi.org/10.1088/0031-9155/59/7/1831.
[62] Fonseca GP, Viana RS, Podesta M, Rubo RA, de Sales CP, Reniers B, et al. HDR 192Ir source speed measurements using a high speed video camera. Med Phys 2015;42:412–5. https://doi.org/10.1118/1.4903286.
[63] Bellezzo M, Baeza JA, Voncken R, Reniers B, Verhaegen F, Fonseca GP. Mechanical evaluation of the Bravos afterloader system for HDR brachytherapy. Brachytherapy 2019;18:852–62. https://doi.org/10.1016/j.brachy.2019.06.005.
[64] Shen C, Gonzalez Y, Klages P, Qin N, Jung H, Chen L, et al. Intelligent inverse treatment planning via deep reinforcement learning, a proof-of-principle study in high dose-rate brachytherapy for cervical cancer. Phys Med Biol 2019;64:115013. https://doi.org/10.1088/1361-6560/ab18bf.
[65] Jaberi R, Siavashpour Z, Aghamiri MR, Kirisits C, Ghaderi R. Artificial neural network based gynaecological image-guided adaptive brachytherapy treatment planning correction of intra-fractional organs at risk dose variation. J Contemp Brachytherapy 2017;9:508–18. https://doi.org/10.5114/jcb.2017.72567.
[66] Peiffert D, Mazeron JJ, Guedea F, Nisin R. Brachytherapy in France in 2002: results of the ESTRO-PCBE questionnaire. Cancer Radiother 2007;11:146–9. https://doi.org/10.1016/j.canrad.2006.12.003.
[67] Guedea F, Venselaar J, Hoskin P, Hellebust TP, Peiffert D, Londres B, et al. Patterns of care for brachytherapy in Europe: updated results. Radiother Oncol 2010;97:514–20. https://doi.org/10.1016/j.radonc.2010.09.009.
[68] Diez P, Aird EGA, Sander T, Gouldstone CA, Sharpe PHG, Lee CD, et al. A multicentre audit of HDR/PDR brachytherapy absolute dosimetry in association with the INTERLACE trial (NCT015662405). Phys Med Biol 2017;62:8832–49. https://doi.org/10.1088/1361-6560/aa91a9.
[69] Palmer AL, Diez P, Gandon L, Wynn-Jones A, Bownes P, Lee C, et al. A multicentre 'end to end' dosimetry audit for cervix HDR brachytherapy treatment. Radiother Oncol 2015;114:264–71. https://doi.org/10.1016/j.radonc.2014.12.006.
[70] Humbert-Vidan L, Sander T, Eaton DJ, Clark CH. National audit of a system for rectal contact brachytherapy. Phys Imag Radiat Oncol 2017;1:1–5. https://doi.org/10.1016/j.phro.2016.12.001.
[71] Nose T, Masui K, Takenaka T, Yamazaki H, Nakata K, Otani Y, et al. An easy and novel method for safer brachytherapy: real-time fluoroscopic verification of high-dose-rate 192Ir source position using a flat-panel detector. J Radiat Res 2019;60:412–5. https://doi.org/10.1093/jrr/rrz013.
[72] Beld E, Seevinck PR, Schuurman J, Viergever MA, Lagendijk JJW, Moerland MA. Development and testing of a magnetic resonance (MR) conditional afterloader for source tracking in magnetic resonance imaging-guided high-dose-rate (HDR) brachytherapy. Int J Radiat Oncol Biol Phys 2018;102:960–8. https://doi.org/10.1016/j.ijrobp.2018.04.066.
[73] Tho D, Beaulieu L. Technical Note: Identification of an optimal electromagnetic sensor for in vivo electromagnetic-tracked scintillation dosimeter for HDR brachytherapy. Med Phys 2019;46:2031–6. https://doi.org/10.1002/mp.13508.
[74] Reniers B, Landry G, Eichner R, Hallil A, Verhaegen F. In vivo dosimetry for gynaecological brachytherapy using a novel position sensitive radiation detector: feasibility study. Med Phys 2012;39:1925–35. https://doi.org/10.1118/1.3693049.
[75] Boutaleb S, Racine E, Fillion O, Bonillas A, Hautvast G, Binnekamp D, et al. Performance and suitability assessment of a real-time 3D electromagnetic needle tracking system for interstitial brachytherapy. J Contemp Brachytherapy 2015;7:280–9. https://doi.org/10.5114/jcb.2015.54062.
[76] Damato AL, Viswanathan AN, Don SM, Hansen JL, Cormack RA. A system to use electromagnetic tracking for the quality assurance of brachytherapy catheter digitization. Med Phys 2014;41:101702. https://doi.org/10.1118/1.4894710.
[77] Kallis K, Kreppner S, Lotter M, Fietkau R, Strnad V, Bert C. Introduction of a hybrid treatment delivery system used for quality assurance in multi-catheter interstitial brachytherapy. Phys Med Biol 2018;63:095008. https://doi.org/10.1088/1361-6560/aabb5a.
[78] The Patient Safety in Radiotherapy Steering Group and Public Health England. 14/12/2019]; Available from: https://www.gov.uk/government/publications/radiotherapy-errors-and-near-misses-data-report.
[79] Derreumaux S, Etard C, Huet C, Trompier F, Clairand I, Bottollier-Depois JF, et al. Lessons from recent accidents in radiation therapy in France. Radiat Prot Dosimetry 2008;131:130–5. https://doi.org/10.1093/rpd/ncn235.
[80] Radiological Protection Act 1991 (Ionising Radiation) Regulations 2019.
[81] Duan J, Macey DJ, Pareek PN, Brezovich IA. Real-time monitoring and verification of in vivo high dose rate brachytherapy using a pinhole camera. Med Phys 2001;28:167–73. https://doi.org/10.1118/1.1339882.
[82] Nakano T, Suchowerska N, McKenzie DR, Bilek MM. Real-time verification of HDR brachytherapy source location: implementation of detector redundancy. Phys Med Biol 2005;50:319–27. https://doi.org/10.1088/0031-9155/50/2/010.
[83] Bati M, Burger J, Cindro V, Kramberger G. Verification of high dose rate 192Ir source position during brachytherapy treatment. Nucl Instrum Methods Phys Res A 2010;617:206–8. https://doi.org/10.1016/j.nima.2009.09.122.
[84] Van Gellekom MPR, Canters RAM, Dankers F, Loopstra A, van der Steen-Banasik EM, Haverkort MAD. In vivo dosimetry in gynecological applications-A feasibility study. Brachytherapy 2018;17:146–53. https://doi.org/10.1016/j.brachy.2017.04.240.
[85] Belley MD, Craciunescu O, Chang Z, Langloss BW, Stanton IN, Yoshizumi TT, et al. Real-time dose-rate monitoring with gynecologic brachytherapy: Results of an initial clinical trial. Brachytherapy 2018;17:1023–9. https://doi.org/10.1016/j.brachy.2018.07.014.
[86] Jamalludin Z, Jong WL, Ho GF, Rosenfeld AB, Ung NM. In vivo dosimetry using MOSkin detector during Cobalt-60 high-dose-rate (HDR) brachytherapy of skin cancer. Australas Phys Eng Sci Med 2019;42:1099–107. https://doi.org/10.1007/s13246-019-00809-7.
[87] Jamalludin Z, Jong WL, Malik RA, Rosenfeld AB, Ung NM. Evaluation of rectal dose discrepancies between planned and in vivo dosimetry using MOSkin detector and PTW 9112 semiconductor probe during (60)Co HDR CT-based intracavitary cervix brachytherapy. Phys Med 2019;69:52–60. https://doi.org/10.1016/j.ejmp.2019.11.025.