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(54) **Title:** QUALITY CONTROL SYSTEM AND METHOD

(57) **Abstract:** The present disclosure relates to methods for analysing in-vivo dosimetry data during radiotherapy. The data relates to positions of radiation sources and dosimeters. The methods result in improved analysis of this data. The data may be used by healthcare professionals to evaluate progress of scheduled events.

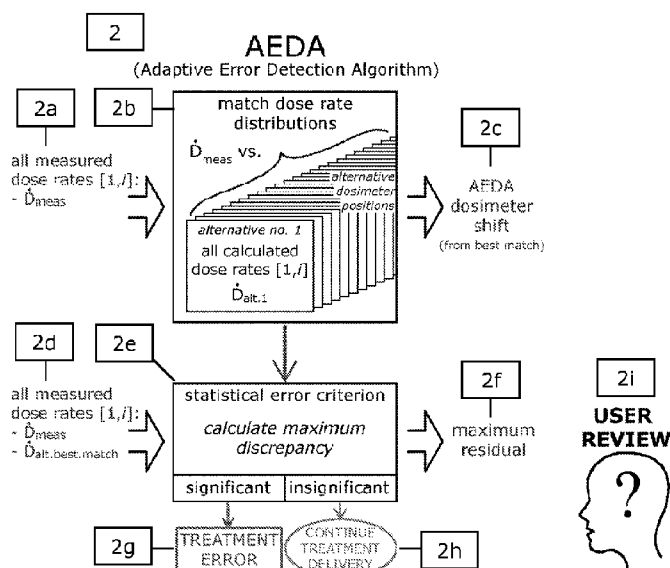


Fig. 2



GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ,
TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU,
TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE,
DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT,
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QUALITY CONTROL SYSTEM AND METHOD

FIELD OF THE INVENTION

The present invention pertains to the field of quality assurance of radiotherapy treatments and related systems, devices, and computer program methods. The present invention further relates to monitoring the delivered dose rates in order to detect potential discrepancies from the planned treatment. In particular, the invention relates to a computer program method for determining whether a potential discrepancy assessment is true or false. The present invention is particularly useful in connection with, but not limited to, brachytherapy.

BACKGROUND OF THE INVENTION

In-vivo dosimetry (IVD) can be implemented as a safety system during radiotherapy in order to identify potential error events where a treatment delivery does not follow a predetermined treatment plan. Such error events may result in the under-dosage of the tumor or excessive dose to organs at risk.

A dosimeter generally comprises a radiosensitive detector device coupled to an electronic readout system for signal processing. The dosimeter suitable for brachytherapy (BT) IVD may be positioned in or near the tumor region in order to monitor the conformity of the measured dose to the treatment plan. The monitoring may be continuously performed. For afterloaded BT, the treatment plan specifies source dwell times and source dwell coordinates throughout the treatment delivery, which have been optimized by medical personnel in order to conform the dose to the tumor volume and spare organs at risk from excessive dose. For BT implementations, the dosimeter signal response depends on the distance between the BT source and the dosimeter, and the BT source strength.

Most afterloaded BT treatment errors originate from human errors which include but are not limited to incorrectly specified source strengths and erroneously connected source transfer guide tubes, while the remainder mainly are related to malfunctions of the equipment which include but are not limited to defect afterloader stepping motor and flaws in the control software, as specified in the International Commission on Radiological Protection (ICRP) reports 86 and 97, and in the International Atomic Energy Agency (IAEA) safety report series 17.

SUMMARY OF THE INVENTION

Medical personnel may employ IVD and related computer program method outputs in order to determine the significance and type of an IVD identified treatment mis-administration. If significant, a treatment error is declared such that there is a risk of under-dosage to the tumor volume and excessive dose to organs at risk. An identified treatment error such as a guide tube swap may result in adjustments followed by a recovered treatment, while errors such as significant catheter mis-reconstructions may warrant treatment termination. The significance of a potential error detection is determined based on the discrepancy between dose rate distributions for a measurement and for calculations of alternative dosimeter positions. A significant maximum discrepancy between the measured and alternative dose rate distributions, declared by a statistical error detection criterion which incorporates all known dose rate measurement and calculation uncertainties, defines the presence of a true treatment error, while an insignificant maximum discrepancy is characterized by the absence of a true treatment error.

The decision regarding a treatment modification, made by a medical professional and not necessarily to be included in the method according to the present invention, involves weighing factors which greatly affect the patient: a decision based on a true error may prevent excessive dose to organs at risk. However, if based on a false error, the treatment termination would cause unnecessary health risks and discomfort for the patient, potentially related to source catheter re-implantation and re-iterated patient scans. Properly incorporated IVD in the clinical routine should therefore include measures that minimize the risk of false errors.

The present disclosure provides an error detection method for quality control of in-vivo BT dosimetry which does not require an accurate a priori knowledge of the dosimeter position, hence no thorough dosimeter reconstruction. In principle, the present disclosure is independent from a priori dosimeter reconstruction. As a result, the method is insensitive to systematic effects which compromise the dosimeter reconstruction which could lead to false error detection.

It is an object of the present invention to provide a reliable method for objectively evaluating data from a measurement. It is also an object of the present invention to provide an analysis result that enables a healthcare professional to evaluate a procedure. It is a further object of the present invention to provide an alternative to the prior art.

Accordingly, the above described object and several other objects are intended to be obtained in a first aspect of the invention by providing a method of evaluating data that may comprise the following. For BT, a set of parameters are obtained from the
5 predefined treatment plan and comprises radiation source positions and the corresponding dwell times.

Particularly, but not exclusively, the invention is advantageous for obtaining a reliable quality evaluation of in-vivo dosimetry data and efficient error detection capacity
10 during radiotherapy. A computer program method is advantageous for its generality which makes it implementable for any point detector capable of measuring time resolved dose rates. The computer program method does not depend on a priori knowledge of the dosimeter position, hence reconstruction of the dosimeter position using patient scan images is not required, which results in the elimination of
15 systematic effects which compromise the dosimeter position acquired during the patient scan. Furthermore, given that the position of the dosimeter is not needed to be reconstructed and that the method only requires a stable dosimeter position in or near the tumor region, the personnel or human induced uncertainties of the dosimeter position reconstruction is eliminated and time investments required by medical
20 personnel gets reduced substantially. Still further, the data driven computer program algorithm provides time updated geometrical feedback of the dosimeter position in three orthogonal directions throughout the treatment delivery, which aids the interpretation of the measured and planned dose rate comparisons.

25 In an embodiment of the method wherein the radiotherapy is external beam radiotherapy (EBRT), typically a single radiation source, external to the patient, will provide the set of radiation source positions in a volume of interest. Thus, in this case, the volume of interest will also include a volume surrounding the patient, to include the positions of the external radiation source as part of a treatment plan.

30

In a second aspect, the invention relates to a dosimetry system which comprises a radiosensitive detector device. Under influence of radiation from the radiation source, the active region of the detector device emits a signal in proportion to the radiation dose absorbed. The detector device is coupled to an electronic readout system for
35 data processing, such that the emitted signal may be translated into radiation parameters relevant for the data analysis. For suitability for BT IVD, the detector probe of the dosimetry system may be appropriately configured in order to acquire a

position in or near the tumor region such that the correspondence between the measured dose and the treatment plan can be properly monitored. Given that the method according to the present invention only requires a stable dosimeter position in or near the tumor region, the dosimeter placement may be performed manually by
5 medical personnel or by a motorized system, e.g. where the dosimeter is attached to a stepping motor in an afterloader.

In a third aspect, the invention relates to a computer program product that is adapted in order to enable a computer system that comprises at least one computer having data storage means and data processing means in connection therewith to perform
10 quality control of the afterloaded BT treatment delivery by means of the computer program method, previously described, and the dosimetry system, also previously described. Such a computer program product may be provided on any kind of computer readable medium, or through a network.

15 The individual aspects of the present invention may each be combined with any of the other aspects. These and other aspects of the invention will be apparent from the following description with reference to the described embodiments.

BRIEF DESCRIPTION OF THE FIGURES

20

The above mentioned method and system and other aspects according to the invention will now be described in more detail with regard to the accompanying figures. The figures show one way of implementing the present invention and is not to be construed as being limiting to other possible embodiments falling within the scope
25 of the attached claim set.

Figure 1 is a schematic flow-chart which outlines the operations of a method according to the present invention.

30 Figure 2 illustrates a computer program algorithm.

Figure 3 illustrates the dose rates measured with the dosimeter and calculated according to the treatment plan (top plots), and the discrepancies expressed in % for each source dwell position (bottom plots). The calculations were made for two IVD
35 implementations, labeled in-vivo case A and B. In bottom plots, the %-representations of 1σ and 2σ limits are shown for comparison.

Figure 4 illustrates the geometric feedback provided by the computer program algorithm in the three orthogonal directions (top plots) and for the total distance (middle plots). The bottom plots show the adaptive error detection algorithm, labeled AEDA, provided by the computer program algorithm, together with the maximum residuals for a static error detection algorithm, labelled SEDA. The plots represent results for in-vivo cases A and B.

Figure 5 illustrates an example of a correctly identified error case that was generated in a simulation of a swap between guide tubes related to ring and 5th needle applicators. The top plot shows the geometric feedback provided by the computer program algorithm for the total distance, referred to as AEDA distance shift. The bottom plot shows the maximum residuals for the adaptive error detection algorithm, labelled AEDA, provided by the computer program algorithm, and for a static error detection algorithm, labelled SEDA.

Figure 6 illustrates an example of a correctly identified false error case that was generated in a simulation of a dosimeter shifted by 5 mm from its original position. The top plot shows that the geometric feedback provided by the computer program algorithm for the total distance, referred to as AEDA distance shift, agrees with the simulated 5 mm dosimeter position shift. The bottom plot shows the maximum residuals for the adaptive error detection algorithm, labelled AEDA, provided by the computer program algorithm, and for a static error detection algorithm, labelled SEDA.

Figure 7 illustrates the pattern agreement for dose rate residuals of in-vivo measurement and a dose rate calculation at the position corresponding to the converged AEDA dosimeter shift for treatment case A.

DETAILED DESCRIPTION OF AN EMBODIMENT

The following description is partially referred to afterloaded BT for cervix cancer. However, it will be appreciated that the method is not limited to this application but general for any afterloaded BT treatment which involve a treatment plan. The method is therefore relevant for afterloaded BT to other organs, including for example prostate, breast, esophagus, etc.

35

In this document, dose rate discrepancies originating from mis-administered treatment procedures will be referred to as true errors, and those from systematic

effects as false errors. True errors include but are not limited to scenarios of incorrectly specified source strength, erroneously connected source transfer guide tubes, defect afterloader stepping motor and flaws in the control software; all of which may result in excessive dose to organs at risk and/or insufficient dose to the tumor, i.e. into injury for the patient and/or an untreated tumor. False errors include systematic effects which compromise the dosimeter reconstruction, and do not result in a treatment delivery significantly different from the pre-defined treatment plan, hence do not result in injury for the patient and at the same time ensures a properly treated tumor. In clinical scenarios, true errors may warrant treatment modification, e.g. treatment termination, while false errors do not. Since the algorithm preferably is applied on a real-time basis, the algorithm is suitable for high dose rate (HDR) BT where timely treatment termination may be crucial for the patient in case of an error. The algorithm provides an improved basis for clinical staff to make a distinction between true and false errors by providing an objective classification of errors in true and false categories. The final decision lies with the clinical staff.

Figure 1 schematically illustrates the operations of a method that constitutes an overall quality control aspect for an afterloaded BT treatment. The data may be evaluated real-time, i.e. during the treatment delivery, and/or for post-treatment processing.

Prior to the treatment delivery, a treatment plan is designed by medically trained personnel for the specific patient based on scanned images of the treatment region or volume, such that tumor volumes and organs at risk volumes can be delineated, and such that inserted source carrying catheters in which the radiation source may dwell can be reconstructed. The scanned images can be acquired with for example computed tomography, magnetic resonance imaging, and/or ultrasound technology. The medical personnel optimizes the treatment plan such that the source positions and corresponding dwell times would result in a conformed radiation dose to the tumor volume and a minimized radiation dose to the organs at risk.

Figure 1 step 1a illustrates a computer program method that retrieves the radiation source positions and the corresponding dwell times from the predefined treatment plan.

Figure 1 step 1b illustrates the provision of stable positioning of the dosimeter probe in or near the treatment volume, which comprises the tumor volume and proximal

organs at risk, or at a site where it is possible to obtain a significantly strong measurement signal induced in the dosimeter by the absorbed dose from the radiation source. Such a provision may be achieved by means of a device that is capable of housing the dosimeter probe in or near the treatment volume, e.g. a catheter and/or
5 a BT needle, and that offers geometric stability throughout the treatment delivery.

A point dosimeter may be used, and Figure 1 step 1c, illustrates that in the simplest embodiment, a single radiosensitive detector device is coupled to an electronic readout system for signal processing. The electronic readout system is further
10 connected to a computer or processing device, such that the data may be exploited by the computer program implementation of a method as described in the present disclosure. The point dosimeter is configured to measure time resolved dose rates at the point of the detector volume, where the dose rates are induced by the presence of a radiation source. For BT implementations, the dosimeter signal response depends on
15 the distance between the BT radiation source and the dosimeter, and the BT radiation source strength.

Given the means for positional stability in or near the tumor region (see Figure 1 step 1b), the AEDA implementation allows for point dosimeter placement procedures
20 performed as by the following examples: (A) a point dosimeter may be placed manually by medical personnel prior to the treatment delivery into a dedicated catheter or a BT needle not intended to house the BT radiation source, (B) a point dosimeter, attached to a dedicated stepping motor in a BT afterloader, may be remotely placed prior to the treatment delivery into a dedicated catheter or a BT
25 needle not intended to house the BT radiation source, and/or (C) a point dosimeter, attached to a dedicated stepping motor in a BT afterloader, may be placed during the treatment delivery inside a BT radiation source carrying needle already used during the treatment.

30 In Figure 1 step 1d a part of the computer program algorithm is executed prior to the treatment delivery. In this step, alternative point dosimeter positions given the constraints of the dosimeter device (see Figure 1 step 1b) are simulated. The positions define a three dimensional geometrical grid along three orthogonal directions, which includes the volume constrained by the dosimeter housing and positions beyond the
35 constraints. The constraints/limits of the dosimeter housing/positioning are defined by the geometrical/positional border within which the dosimeter position may reside. Dose rates and positional uncertainties are calculated for each alternative dosimeter

position, such that dose rate distributions could be constructed at any given time during the treatment.

In Figure 1 step 1e, dose rate measurements are performed with the point dosimeter
5 (see Figure 1 step 1c) during the BT treatment delivery.

In Figure 1 step 1f the computer program algorithm includes a data driven adaptive procedure step including matching the measured dose rate distribution generated from all delivered dwell positions during the treatment with those of all alternative
10 dosimeter positions (see Figure 1 step 1d). The matching that results in the best dose rate correspondence between measurement and simulated alternatives provides the most likely position of the point dosimeter. The inventors realize that many different analysis methods are applicable for performing this matching, such as chi-square fitting, Kalman filters, Bayesian analysis, decision trees, etc., without deviating from
15 the scope of the invention.

In an alternative embodiment of the step 1f, matching may be performed on the measured dose rate distribution generated from only a subset of the delivered dwell positions during the treatment. In this way, temporal errors, e.g. due to a shift of the
20 dosimeter during treatment may be detected. However, in order to provide a sufficiently high precision in the likely radiation source positions, it is advantageous to employ simultaneous dosimetry data from multiple point dosimeters, such as two or three dosimeters. In this way, redundancy problems in determining the likely positions of the radiation sources may be alleviated.

25

In step 1g in Figure 1, the dose rates of all delivered dwell positions for the measurements and the calculation corresponding to the most likely position of the point dosimeter are compared by means of a dedicated error decision protocol. Furthermore, the most likely position of the point dosimeter provides a geometrical
30 feedback which aids the assessment whether the point dosimeter is positioned within the constraints of the dosimeter housing. The comparison and the geometrical feedback aids the assessment of whether a potentially detected error corresponds to a true or a false error in the treatment delivery.

35 Figure 2 further illustrates a possible implementation of a computer program algorithm, which in a data driven approach adapts the point dosimeter position to the simulated alternatives (see Figure 1 step 1d) rather than relying on a single a priori

point dosimeter reconstruction. The advantage with this approach is that the error detection is not affected by systematic effects which may compromise an a priori point dosimeter reconstruction. As a result, the algorithm, also referred to as an adaptive error detection algorithm (AEDA), provides a way of detecting dose rate discrepancies
5 originating from mis-administered treatment procedures rather than from systematic effects. Hence, the AEDA provides with confidence in the error declaration.

Dosimeter Position Adaptation

10 The AEDA exploits dose rates for individual source dwell positions measured with a point dosimeter, and those calculated for the simulated alternatives (see Figure 1 step 1d).

Based on experimentally supported data the dose rates and dose rate uncertainties
15 were calculated for each simulated point dosimeter position and for all positions acquired by the radiation source such that cumulated dose rate distributions could be constructed at any given time during the treatment delivery.

Sufficient accuracy of the dose rate calculations may be achieved by means of proper
20 calculation protocols, such as the TG-43 protocol, Rivard et al., Med. Phys. 31, 633–674 (2004), and/or Monte Carlo techniques. Rather than using dose rates for the comparison between the measured response of the point dosimeter and the calculations of the simulated alternative dosimeter positions, other surrogates for the dosimeter response could be used depending on the dosimeter technology
25 implemented, e.g. optical signal strength, electrical signal strengths, etc. For the data presented in e.g. Figure 3, dose rates measured in the unit Gy/s were used.

The data driven adaptive approach of the AEDA involves comparing all measured dose rates at any given time during the treatment delivery (see Figure 2 step 2a), with all
30 calculated dose rates for each one of the simulated alternative dosimeter positions (see Figure 2 step 2b and Figure 1 step 1d). The comparison that results in the best match corresponds to the most likely point dosimeter position with respect to a reference point, e.g. the tip of the dosimeter housing (see Figure 1 step 1b). The most likely point dosimeter position will in this document be referred to as the AEDA
35 dosimeter distance (see Figure 2 step 2c). The best match between the measured and the set of alternative dose rate distributions thus corresponds to the alternative dose

rate distribution within the set with the greatest resemblance to the measured dose rate distribution.

As an example, the alternative dosimeter positions may be simulated in a volume encompassing the dosimeter housing (see Figure 1 step 1b) along three orthogonal directions with respect to a radiation source carrying catheter reconstructed in the treatment plan (see Figure 1 step 1a):

- 1) the radial direction defined by the vector between the dosimeter and the closest point on the axis of the tandem applicator,
- 2) the longitudinal direction defined by the axis of the tandem applicator, and
- 3) the sideways direction which was orthogonal to the radial and longitudinal directions.

These simulated alternative dosimeter positions may cover both the volume constrained by the dosimeter housing and volume beyond the dosimeter housing, where the dosimeter cannot reside. In a study, these simulated alternative dosimeter positions defined a cuboid in which two positions were separated by 1 mm, and that had the dimensions ± 12 mm, ± 20 mm, and ± 12 mm in radial, longitudinal, and sideways directions, respectively, about the tip of the dosimeter housing.

The data driven matching between dose rate distributions for the measurement and the simulated alternatives was quantified with the χ^2 metric,

$$\chi^2 = \sum_{i=1}^N \left(\frac{\dot{D}_{m,i} - \dot{D}_{s,i}}{\sqrt{\sigma_{m,i}^2 + \sigma_{s,i}^2}} \right)^2 / (N - 1)$$

where i represents one out of the N source dwell positions analyzed, $\dot{D}_{m,i}$ and $\dot{D}_{s,i}$ the measured and simulated dose rates, respectively, for the i^{th} dwell position, and $\sigma_{m,i}$ and $\sigma_{s,i}$ their standard uncertainties. The smaller the χ^2 , the better the match between dose rate distributions. Furthermore, the comparison that yielded the best match provided the most likely dosimeter offset from the reference point, i.e. the AEDA dosimeter distance.

The use of the chi2 metric as described comprises one method to obtain the strongest dose rate correspondance between the measurement and the calculations for the simulated alternative dosimeter positions. Other methods may be used.

Criterion for Error Detection

An error detection criterion was employed in order to determine whether discrepancies between dose rates of the measurement and best match calculation indicated a potential treatment error.

5

In order to allow for timely treatment error detection, time resolved dose rate information was necessary, such that the error assessment could be performed for each individual radiation source dwell position, e.g. at a 1 second time interval.

- 10 One way to assess the dose rate distributions is to apply a statistically based calculation, described in C. E. Andersen et al., Med. Phys. 36, 5033-5043 (2009). The statistically based calculation quantifies the significance of the discrepancies between the measured and best match calculated dose rates. The significance was judged according to an error criterion in order to determine whether a treatment error was
15 declared.

The dose rate discrepancy was quantified in terms of the quadrature sum of standard uncertainties for measured and best match calculated dose rates. An example error criterion, is to declare a potential treatment error if the discrepancy was greater than
20 two quadrature sums.

The total standard uncertainty of the measured dose rate was estimated as the quadrature sum of standard uncertainties for imperfections in the calibration coefficients (including the stem suppression technique, and the angular and distance-
25 related energy dependencies of the dosimeter material), the counting statistics of the readout count rates, and the influence on the readout count rate by temperature variations (-0.5%/K C. E. Andersen et al., Radiat. Meas. 43, 948-953 (2008)). In a study, the standard uncertainty for calculated dose rates corresponded to the influence from reconstruction uncertainties of source and dosimeter probe positions
30 (referred to as the positional uncertainty).

In the study, the positional uncertainty constituted the dominant component in the uncertainty budget. The magnitude of the positional uncertainty was affected by the image quality of the patient scan used for the treatment plan - the poorer the quality,
35 the larger the uncertainty. If an error detection method based on the a priori reconstructed dosimeter position was used, i.e. if the measured dose rate was compared with dose rate calculations based on a fixed a priori reconstructed

dosimeter position, the positional uncertainty would be dependent on the image quality of the patient scan. Given the dominant role of the positional uncertainty in the error detection criterion, as described, the sensitivity and performance of such an error detection method would worsen the poorer the image quality would be.

- 5 However, since the AEDA is independent from the a priori dosimeter reconstruction, the uncertainty calculation for the AEDA and its error detection capability is not affected by the image quality of the patient scan. Rather, the positional uncertainty for the AEDA depends on the separation distance between each simulated alternative dosimeter position – the smaller the distance the smaller the positional uncertainty.

10

Maximum residual

In the final part of the AEDA, and after the point dosimeter position adaptation procedure, the cumulated dose rate distributions for the measurement and best match
15 calculation were assessed according to the previously described statistical error criterion, in order to determine whether a potential treatment error could be declared.

- Residuals were calculated for each delivered dwell position for dose rate distributions of the measured and the best match calculation (see Figure 2d), and assessed with
20 the statistical error criterion (see Figure 2e). The maximum of all calculated residuals was provided (see Figure 2f).

User Review

- 25 The AEDA dosimeter distance (see Figure 2 step 2c) and the maximum residual (see Figure 2 step 2f) were subject to user review by medical personnel (see Figure 2 step 2i), in order to aid the decision making regarding the integrity of the treatment delivery. In other words, the user review corresponded to using the AEDA as a guidance to a potential treatment modification. The decisions to be made were
30 whether a true treatment error could be declared (see Figure 2 step 2g) or if the treatment delivery could proceed (see Figure 2 step 2h). A true treatment error would warrant a modification or a termination of a treatment delivery, while the absence of a true treatment error would allow the treatment to proceed without interruption.
- 35 The decision making could be based on the following reasoning, all of which in principle could be automatized in a computer program algorithm.

A true treatment error indication was declared

- if the maximum discrepancy was significant, hence broke the statistical error criterion, regardless of the AEDA dosimeter distance output, or
- if the AEDA dosimeter distance represented a dosimeter position outside the constraints of the dosimeter housing, regardless of the maximum discrepancy output.

For both scenarios, the AEDA was unable to identify a potential dosimeter position within the constraints of the dosimeter housing which matched the measured dose rate distribution. Such scenarios would be expected, e.g. if irradiation source transfer guide tubes were erroneously connected and/or if irradiation source catheters were mis-positioned or mis-reconstructed.

No indication of a true treatment error was declared if the maximum discrepancy was insignificant and the AEDA dosimeter distance represented a point dosimeter position within the constraints of the dosimeter housing.

Evaluation of the AEDA

As an evaluation of the method according to the present disclosure, comparisons have been performed for a patient treatment implementation and for treatment simulations
5 with a traditional static error detection algorithm, SEDA.

The SEDA included comparing the measured dose rate distribution with that of the original treatment plan and an originally reconstructed point dosimeter position, and verifying whether the maximum residual broke the statistical error criterion. The SEDA
10 was therefore highly dependent on the original a priori reconstruction of the point dosimeter position.

In-vivo dosimetry implementation

15 Both AEDA and SEDA analyses were applied for two patient treatment cases. The SEDA implementation was based on an a priori point dosimeter reconstruction performed by trained personnel. For one of the SEDA implementations, significant discrepancies had been declared by the statistical error criterion (case A), while no potential errors had been declared for the other (case B). AEDA and SEDA were
20 applied on both treatment cases, in order to examine whether true or false errors were indicated based on the a priori point dosimeter reconstruction.

Real-time IVD with a fiber-coupled Al₂O₃:C dosimeter had been performed during PDR BT treatments (20 pulses-per-fraction) of locally advanced cervical cancer at
25 Aarhus University Hospital in Aarhus, Denmark. MRI guided adaptive BT was delivered with a combined intracavitary/interstitial applicator, where six interstitial needles were inserted through a needle-cap attached on a plastic tandem-ring applicator, as described by L. Fokdal et al., Radiother. Oncol. 107, 63–68, (2013). The applicator reconstruction and treatment planning procedures incorporated have previously been
30 described by J. C. Lindegaard, et al., Int. J. Radiation. Oncology. Biol. Phys. 71, 756–764 (2008) and S. Haack et al., Acta. Oncol. 49, 978–983 (2010). Irradiations were performed using a Varian GammaMed Plus PDR afterloader containing an ¹⁹²Ir PDR source.

35 Treatment case (A) incorporated 11 source dwell positions in the tandem applicator, 7 in the ring, and 2, 1, 1, 1, 3, and 4 in needles 1–6, respectively. Treatment case (B) incorporated 13 source dwell positions in the tandem applicator, 9 in the ring, and 4,

4, 4, 3, 6, and 4 in needles 1–6, respectively. Estimated standard uncertainties of the reconstructed (x, y, z)-positions for treatment cases (A) and (B) were equal to (1.0,1.0,1.5) mm and (1.0,1.0,1.0) mm, respectively.

- 5 The dosimeter probe was a $2 \times 0.5 \times 0.5$ mm³ Al₂O₃:C crystal that was fiber-coupled to a 15 m long fiber-cable. The radioluminescence emitted from the Al₂O₃:C crystal, and transmitted through the fiber-cable, was collected by photomultiplier tubes (PMTs). The Al₂O₃:C crystal was irradiated prior to IVD in order to provide a maximized and stable radioluminescence that was linear in both PDR and HDR dose levels. The stem
10 signal background was suppressed by weighting optically filtered channel read-outs according to an adapted technique, developed for fiber-coupled scintillator external beam dosimetry by Fontbonne et al. The calibration accounted for the 0.2%/K temperature influence on the Al₂O₃:C crystal response due to the temperature difference between the calibration phantom and the patient. The dose algorithm
15 implemented corrections for energy dependence of the high-Z Al₂O₃:C material.

Dosimetry implementation in clinical workflow

- Dosimetry in the tumor region was facilitated with a standard plastic source catheter
20 which was attached to the base of the tandem applicator. The autoclaved catheter housed the dosimeter probe throughout the treatment delivery and assured no patient contact with the probe.

- The dosimeter probe position was determined from MR/CT scan image reconstructions
25 of a copper sulfate filled tube inserted in the dosimeter housing. The dosimeter probe was inserted prior to the treatment delivery such that its tip touched the bottom of the dosimeter housing. The Al₂O₃:C crystal position, i.e. the a priori point dosimeter position for the SEDA analysis, was deduced by subtracting the known distance between the dosimeter probe tip and the crystal's center-of-mass from the identified
30 bottom of the dosimeter housing. Source and Al₂O₃:C crystal position coordinates, and the source dwell times, were retrieved from the pre-defined treatment plan, such that originally reconstructed dose rates could be calculated according the TG-43 protocol.

- 35 Figure 3 illustrates measured and planned dose rates at 1s time resolution (top plots), and discrepancies expressed in % for each dwell position (bottom plots), for treatment cases (A) and (B), where the planned dose rates represent those calculated based on

the a priori dosimeter reconstruction. The %-representations of 1σ and 2σ limits are shown for comparison. Discrepancies between measured and planned dose rates show that the 2σ error criterion was broken for treatment case (A) at the 13th dwell position while no errors were declared for case (B). Furthermore, the σ limits show
5 that error criteria defined by flat %-discrepancies would not be appropriate for BT.

AEDA dosimeter distances and maximum residuals for SEDA and AEDA analyses are shown for treatment cases (A) and (B) in Figure 4. For treatment cases (A) and (B), AEDA dosimeter distances for each orthogonal direction are shown in top plots, AEDA
10 dosimeter distances for the total distance in middle plots, and maximum residuals for SEDA and AEDA analyses are shown in bottom plots.

Referring to Figure 4, the converged AEDA dosimeter distances for treatment cases (A) and (B) indicated that discrepancies originated from dosimeter mis-reconstructions
15 by 4.4 mm and 2.4 mm, respectively. For both treatment cases, the positions obtained with the AEDA were consistent with constraints of the dosimeter shift set by the dosimeter housing. For instance, in treatment case (A), the proposed adapted dosimeter position represented a point along the dosimeter housing identified from the patient scan. For treatment case (A), the maximum residual analyses indicated
20 that the SEDA detected error was attributed to a mis-positioned dosimeter according to the AEDA analysis, i.e. the error detected by the SEDA corresponded to a false error case which was possible to identify only with the AEDA. For treatment case (B), both SEDA and AEDA analyses deduced maximum residuals below the 2σ error criterion. The maximum residual for the SEDA analysis was obtained for the first dwell
25 position in the treatment. The discontinuity in the maximum residual for the AEDA analysis at the 14th dwell position correctly indicated a small but systematic offset in tandem and ring applicator reconstructions.

Simulated scenarios: true and false errors

30

The ability of both AEDA and SEDA analyses to correctly identify true and false errors was tested for simulated treatment scenarios under the ideal dosimetry conditions set by the TG-43 protocol (e.g. full scatter conditions and absence of energy dependence for the dosimeter material).

Treatment plan (A) was regarded as the original plan. Simulated data representing either true or false error scenarios were calculated from modifications of the original plan. The simulated error scenarios corresponded to

- i. true errors: swaps between two guide tubes (all permutations),
- 5 ii. true errors: reconstruction errors of individual needle positions by $\pm(3, 5, 7, 10, 15, 20)$ mm in radial, longitudinal or sideways directions,
- iii. false errors: shifted dosimeter positions by $\pm(1, 3, 5)$ mm in 18 arbitrary directions about the original reconstruction.

For error scenarios (ii), the longitudinal direction was defined by the axis of each
 10 needle, the radial direction by the vector between the crystal and the closest point on the needle axis, and the sideways direction by the direction orthogonal to radial and longitudinal directions. All dose rates for the simulated data were assumed to be subject to a flat 3.3% measurement uncertainty, which represented that of the in-vivo measurements. True error scenarios (i) represented possible connection errors made
 15 in the treatment room by the clinical staff, and (ii) mis-reconstructions during the treatment planning stage and/or source catheter drifts during the treatment delivery. False error scenarios (iii) represented a dosimeter probe mis-positioned or mis-reconstructed with respect to the original reconstruction.

20 **Simulated true errors: guide tube swaps**

Table I shows that all guide tube swaps involving tandem or ring applicators were identified with both SEDA and AEDA. The efficient error identification was attributed to the unique applicator orientations and distances to the dosimeter with respect to
 25 those of the remaining applicators.

However, when only needles were involved, some errors were not identified neither with SEDA or AEDA. Unidentified swaps corresponded to scenarios where the needles affected were relatively symmetric about the crystal position, or when the source
 30 sequences for the corresponding channels, i.e. first dwell position's distance from needle tip and the number of dwell positions, were similar.

Table I also shows that most AEDA and SEDA detected guide tube errors were immediate, meaning that the errors were identified within 1 dwell position from the
 35 onset of the error.

Table I. Errors detected with SEDA and AEDA analyses of all 28 possible swap simulations between two guide tubes for in-vivo case (A).

Test conditions		SEDA		AEDA	
applicators involved	total # swaps	# errors detected	# immediate detections	# errors detected	# immediate detections
tandem or ring	13	13	13	13	9
needles only	15	11	7	10	5

- 5 Figure 5 illustrates an example of immediate AEDA detection of a simulated swap between guide tubes related to ring and 5th needle applicators. The top plot shows AEDA distance shift and the bottom plot the maximum residuals for SEDA and AEDA analyses.

10 Simulated true errors: individual needle shifts

- Table II shows needle reconstruction errors identified with SEDA and AEDA analyses. The error identification efficiency was larger when the needles were shifted radially and longitudinally rather than sideways, since the change in total distances between
15 the dosimeter and source positions generally were smaller for sideways shifts than the shifts in orthogonal directions.

- Table II. Errors detected with SEDA and AEDA analyses for simulated needle reconstruction errors in one out of the three orthogonal directions (radial, longitudinal
20 and sideways) by $\pm 20, \pm 15, \pm 10, \pm 7, \pm 5$, and ± 3 mm.

Test conditions		SEDA			AEDA		
needle direction	total # shifts	# errors detected	# immediate detections	minimum shift [mm]	# errors detected	# immediate detections	minimum shift [mm]
radial	48	33	31	5	28	25	5
longitudinal	48	28	28	7	24	23	10
sideways	48	12	8	15	10	8	15

Simulated false errors: dosimeter shifts

- The responses of SEDA and AEDA are here used for analyzing simulated false error
25 scenarios represented by dosimeter shifts about the original reconstruction and are summarized in Table III. The results show that the AEDA analysis correctly disregards all false errors while the SEDA analysis identifies them as true errors. Furthermore,

the converged AEDA distance shift agrees with the simulated dosimeter shift within 0.8 mm.

Table III. SEDA and AEDA responses to false error simulations corresponding to 5 dosimeter shifts about the original reconstruction by 1, 3, and 5 mm.

<u>Test conditions</u>		<u>SEDA</u>		<u>AEDA</u>		
offset [mm]	# simulated positions	# false errors	maximum residual	# false errors	maximum residual	converged offset
1	18	0	0.6σ	0	0.4σ	[1.0, 1.4] mm
3	18	3	2.9σ	0	0.3σ	[2.8, 3.0] mm
5	18	12	12.1σ	0	0.5σ	[4.2, 5.7] mm

Figure 6 shows an example of SEDA and AEDA responses to a simulated false error for treatment case (A), where the dosimeter was shifted by 5 mm. The top plot shows AEDA distance shift and the bottom plot the maximum residuals for SEDA and AEDA analyses.

Simulated reconstruction

Figure 7 shows the pattern agreement between dose rate residuals of the in-vivo measurement for treatment case (A) and a TG-43 calculation at the position corresponding to the converged AEDA dosimeter shift. Assuming that applicators were reconstructed accurately, the pattern agreement indicated (a) the in-vivo point dosimetry was able to resolve positional shifts using the AEDA, and (b) that the in-vivo data quality was comparable with TG-43 conditions, despite corrections for the $\text{Al}_2\text{O}_3\text{:C}$ dosimeter material's energy and temperature dependence. Similar agreement would therefore be expected using organic scintillator probes despite their recently established temperature dependence.

Summary

In summary, the present disclosure provides an adaptive error detection algorithm (AEDA) which provides basis for determining whether significant dose rate discrepancies identified with real-time in-vivo point dosimetry during afterloaded brachytherapy (BT) is caused by a mis-positioned dosimeter (false error) or is caused by errors in the treatment delivery, e.g. interchanged guide tubes or mis-placed needles (true errors). The data driven AEDA incorporates dose rates for individual

dwell positions, and can therefore be implemented for dosimetry systems that provide time resolved dose rate measurements. A study performed by the inventors has shown that the AEDA correctly identified both true and false error scenarios, relying on positional stability for the dosimeter rather than positional accuracy, and that the
5 SEDA was unable to distinguish false from true errors.

It is noted that error detection capacities for existing error detection methods, in contrast to the present disclosure, are strongly dependent on a high level of accuracy of the a priori reconstructed dosimeter position. To this end, existing error detection
10 methods are time consuming, require significant attention by medically trained personnel, set specific demands on the clinical workflow, and/or are vulnerable to systematic errors which compromise the original reconstructed dosimeter position. As a result, existing error detection methods are vulnerable to flawed implementations which would compromise the integrity of error detection declarations, hence
15 potentially result in false positive or false negative error detections and erroneous conclusions regarding the treatment delivery.

This is in contrast to the present disclosure, which only requires a stable dosimeter position in or near the tumor region and a reconstructed reference point along the
20 dosimeter housing in order to provide with basis for determining whether significant dose rate discrepancies represent true or false errors. As already stated, the AEDA implementation allows for point dosimeter placement procedures performed as by the following examples: (A) a point dosimeter may be placed manually by medical personnel prior to the treatment delivery and after the patient scan into a dedicated
25 catheter or a BT needle not intended to house the BT radiation source, (B) a point dosimeter, attached to a dedicated stepping motor in a BT afterloader, may be placed prior to the treatment delivery and after the patient scan into a dedicated catheter or a BT needle not intended to house the BT radiation source, and/or (C) a point dosimeter, attached to a dedicated stepping motor in a BT afterloader, may be placed
30 during the treatment delivery inside a BT radiation source carrying needle already, or not presently, used during treatment. As a result, the present disclosure allows for flexibility in its implementation, without significant modification of existing clinical workflow and without significant added time investments by medical personnel. It is noted by the inventors that the required level of accuracy for the reconstructed
35 reference point in the dosimeter housing can be reached without significant time investments by medical personnel for insertion method (A) and that no time investment is required for insertion methods (B) and (C).

The above describes how to employ a single dosimeter. The method may be expanded with a second, or even more, dosimeters. The calculations may then be performed for each of the positions of the dosimeters. This is also contemplated to improve the
5 AEDA true error detection capability, e.g. for scenarios where the positions of a first and a second dosimeter are such that the direction of a source catheter displacement generates an insignificant change in dose for the first detector but significant for the second and therefore resulting in a detected true error. This is further contemplated to increase the reliability of the measurements and thereby also possibly decreasing the
10 time needed to identify an error situation. In some embodiments of the method, measurements from two or more dosimeters may also be used to calculate positions of the radiation source by means of a localization method, e.g. triangulation.

The invention can be implemented by means of hardware, software, firmware or any
15 combination of these. The invention or some of the features thereof can also be implemented as software running on one or more data processors and/or digital signal processors.

The individual elements of an embodiment of the invention may be physically,
20 functionally and logically implemented in any suitable way such as in a single unit, in a plurality of units or as part of separate functional units. The invention may be implemented in a single unit, or be both physically and functionally distributed between different units and processors.

25 Although the present invention has been described in connection with the specified embodiments, it should not be construed as being in any way limited of the presented examples. The scope of the present invention is to be interpreted in the light of the accompanying claim set. In the context of the claims, the terms "comprising" or "comprises" do not exclude other possible elements or steps. Also, the mentioning of
30 references such as "a" or "an" etc. should not be construed as excluding a plurality. The use of reference signs in the claims with respect to elements indicated in the figures shall also not be construed as limiting the scope of the invention. Furthermore, individual features mentioned in different claims, may possibly be advantageously combined, and the mentioning of these features in different claims does not exclude
35 that a combination of features is not possible and advantageous.

Claims

1. A method of evaluating in-vivo dosimetry data during radiotherapy comprising the steps of:
 - providing a set of radiation source positions in a volume of interest,
 - providing a point dosimeter configured to detect radiation from the radiation source positions,
 - measuring dose rates from the radiation source positions over a period of time,
 - registering and evaluating time resolved dosimeter response to absorbed dose over the period of time,
 - reconstructing positions of the radiation source positions relative to the dosimeter position based on the measured dose rates,
 - detecting errors of the radiation source positions based on the reconstructed positions, and
 - determining whether detected errors constitute true or false error.
2. The method according to claim 1, further comprising providing a schedule including a set of radiation source time intervals defining when each radiation source of the set of radiation sources are to be active in the volume of interest.
3. The method according to claim 1 or 2, wherein the reconstruction of the radiation sources comprises:
 - calculating, based on the set of radiation source positions, alternative dose rate distributions, or dosimeter responses, for a number of dosimeter positions,
 - determining if most likely dosimeter position lies within our outside constraints of dosimeter housing so as to establish a true error or false error, respectively, and
 - determining if maximum discrepancy of dosimeter to calculated dose rate distribution is significant or insignificant so as to establish a true error state or false error state, respectively.
4. The method according to claim 2 and 3, wherein the alternative dose rate distributions, or dosimeter responses, are calculated for the specific periods of time where the radiation sources are active.
5. The method according to claim 3 or 4, wherein the alternative dose rate distributions is calculated for a set of dosimeter positions defined along three planes where the surface normal of two planes are perpendicular.

6. The method according to any one of claims 1-5, wherein the step of detecting errors of the radiation source positions includes comparing measured dose rate with a set of simulated dose rates for a multitude of dosimeter positions.
7. The method according to claim 6, further comprising establishing, provided that the best match between the set of simulated dose rates and the measured dose rate results in a significant maximum discrepancy, a true error state.
8. The method according to claim 6, further comprising establishing, provided that the best match between the set of simulated dose rates and the measured dose rate results in a dosimeter position outside the constraints of dosimeter housing, a true error state.
9. The method according to claim 6, further comprising establishing, provided that the best match between the set of simulated dose rates and the measured dose rate results in an insignificant maximum discrepancy and results in a dosimeter position within the constraints of dosimeter housing, a no error state.
10. The method according to any one of claims 4-7, further comprising provided there is a match between one of the set of simulated dose rates and the measured dose rate using the dose rate distributions as criterion for establishing a new dosimeter position.
11. The method according to claim 10, wherein the new dosimeter position is established relative to the positions of the radiation source.
12. The method according to any one of the preceding claims, wherein the method further comprises the steps of providing at least a second point dosimeter configured to detect radiation from the radiation sources, and wherein the method comprises further reconstructing a radiation source position relative to the dosimeter positions by a localization method based on the measured dose rates from the point dosimeter and the at least second point dosimeter.
13. An apparatus receiving data from an in-vivo radiation dosimeter and having a data base comprising data relating to a set of radiotherapy radiation source positions, the apparatus having a processor being adapted to measuring dose rates from

radiotherapy radiation sources over a period of time using the dosimeter and the processor adapted to perform a reconstruction of positions of the radiation sources based on the measured dose rates, and the processor further adapted to detecting errors of the radiation source positions based on the reconstructed positions.

14. The apparatus according to claim 13, wherein the processor is adapted to calculate, based on the set of radiation source positions alternative dose rate, distributions for a number of positions of dosimeter, and

the processor being adapted to determine if maximum discrepancy of dosimeter to calculated dose rate distribution is significant or insignificant so as to establish a true error or false error, respectively.

15. The apparatus according to any one of the claims 13-14, wherein the apparatus is adapted to initiate an alarm after establishing a true error of the radiation source positions.

16. The apparatus according to any one of the claims 13-15, wherein the processor is further adapted to perform any one of the steps defined in the claims 2-12.

1/6

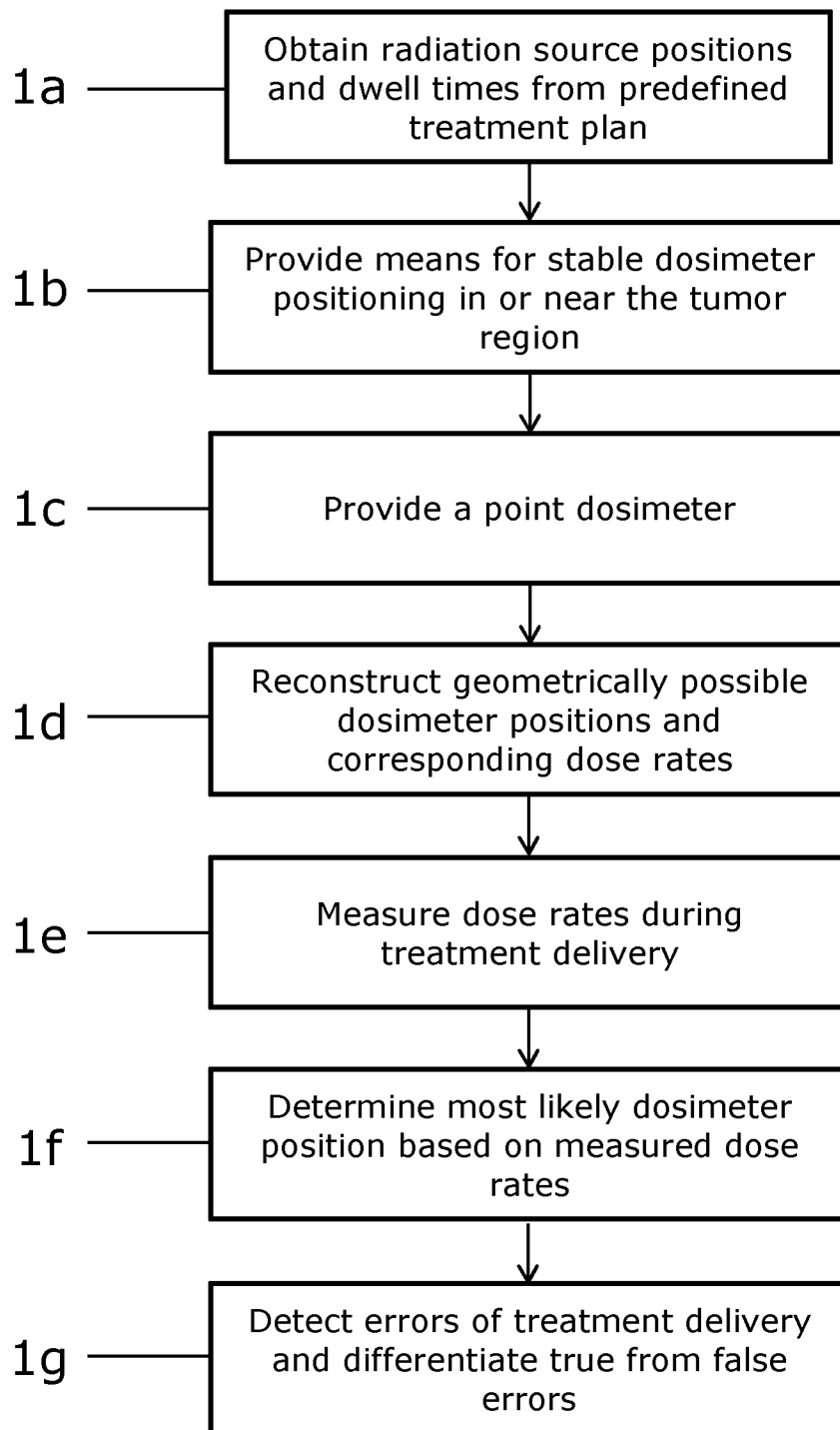


Fig. 1

2/6

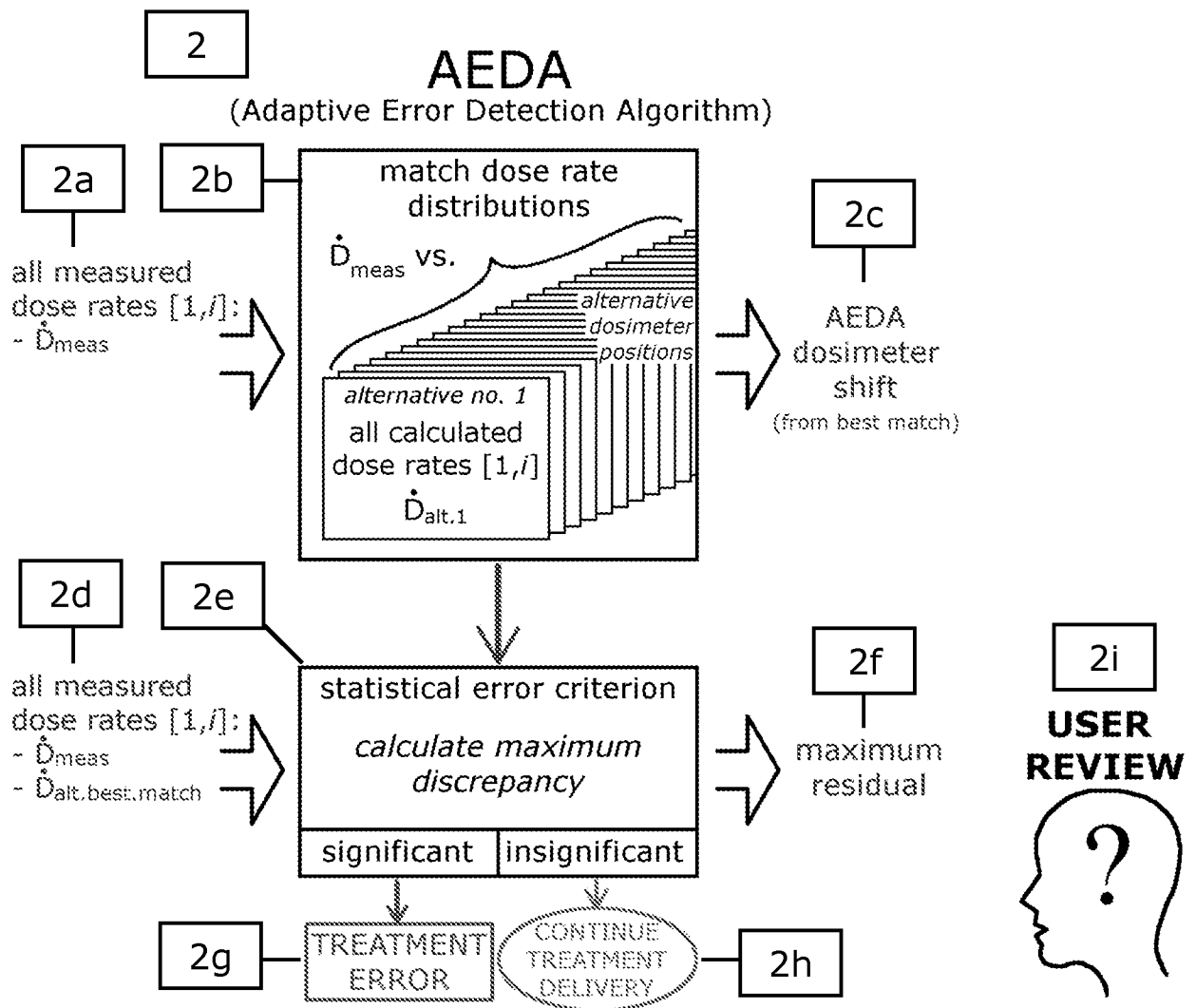


Fig. 2

3/6

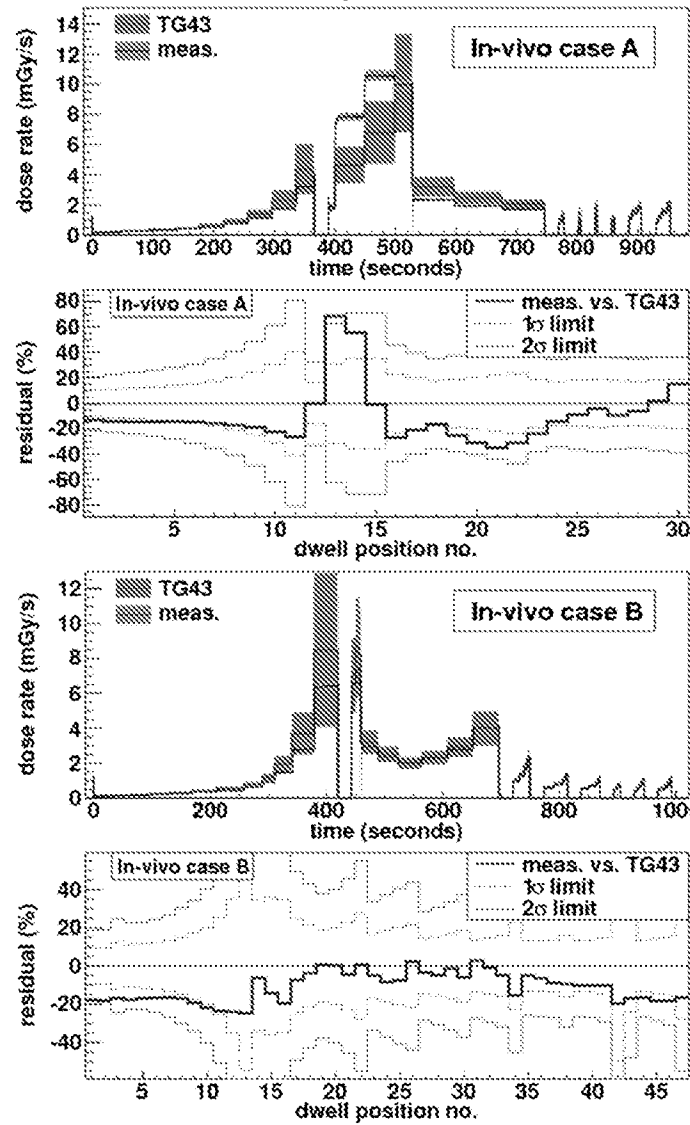


Fig. 3

4/6

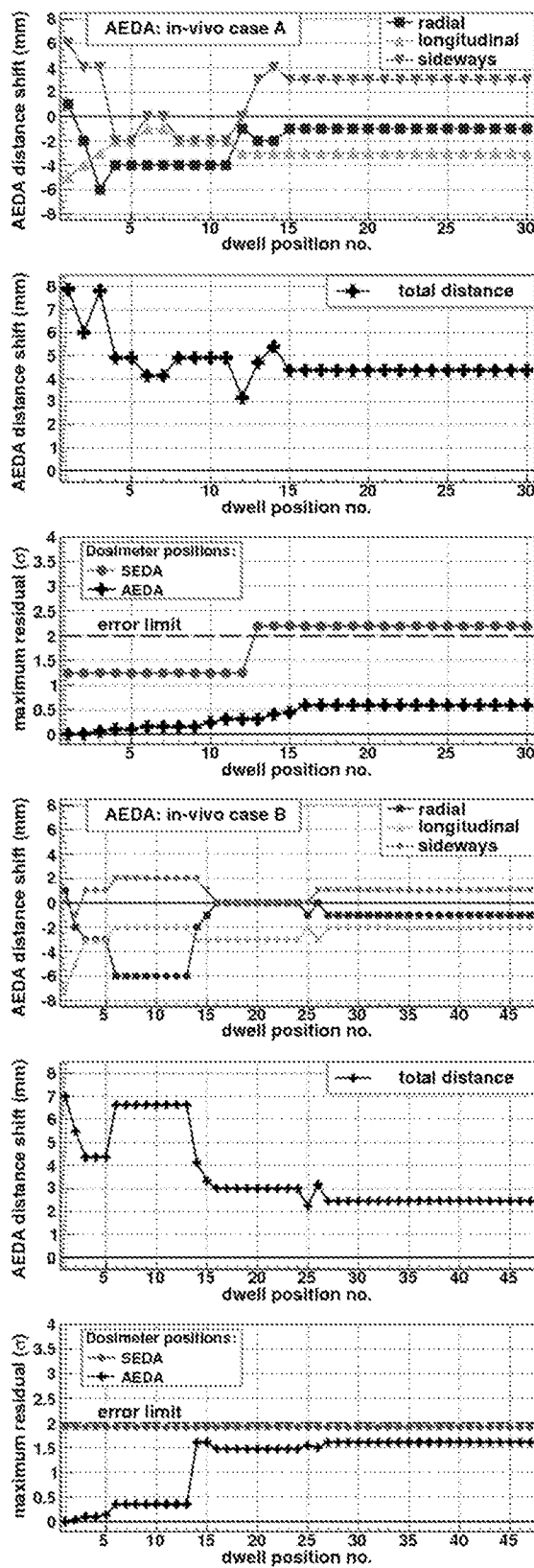


Fig. 4

5/6

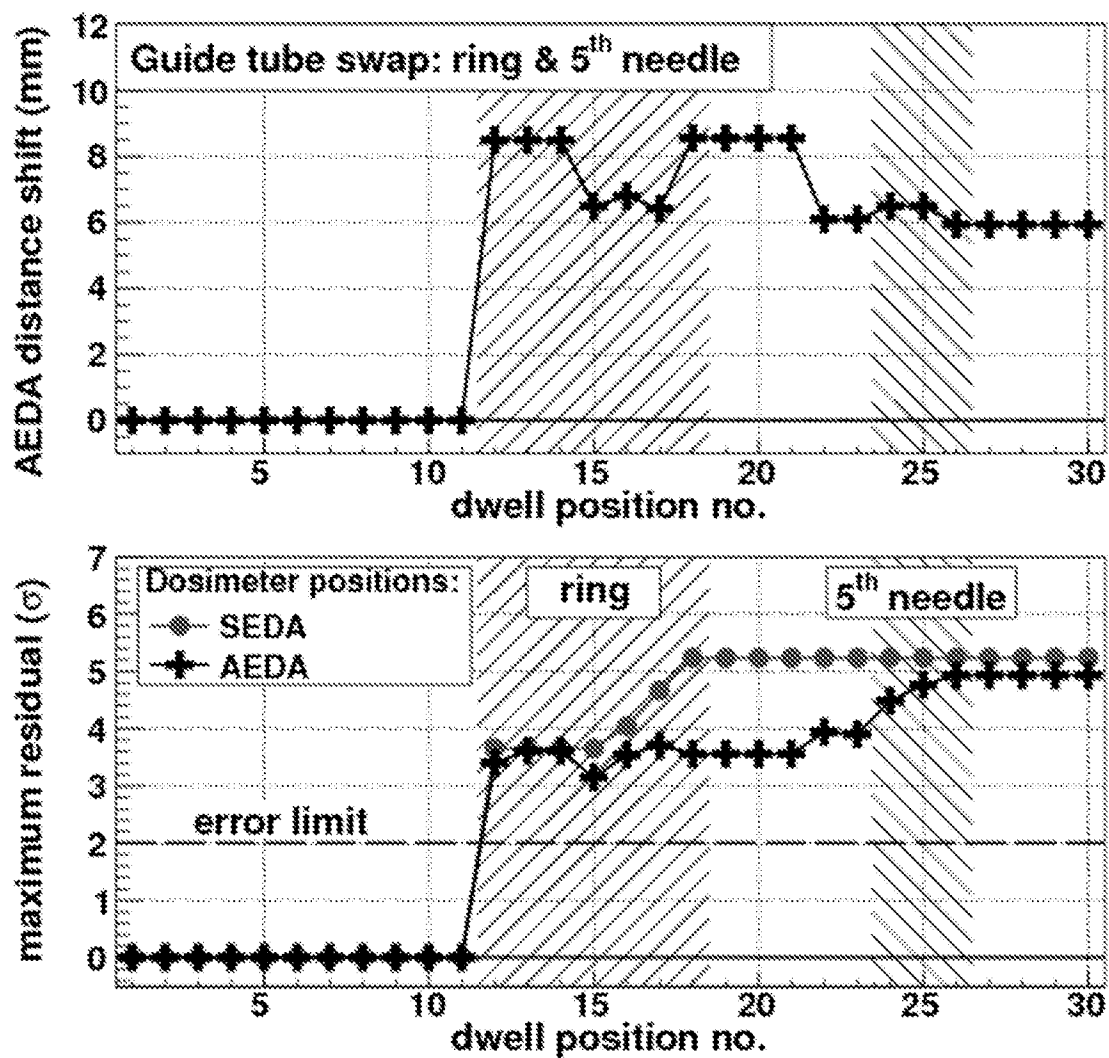


Fig. 5

6/6

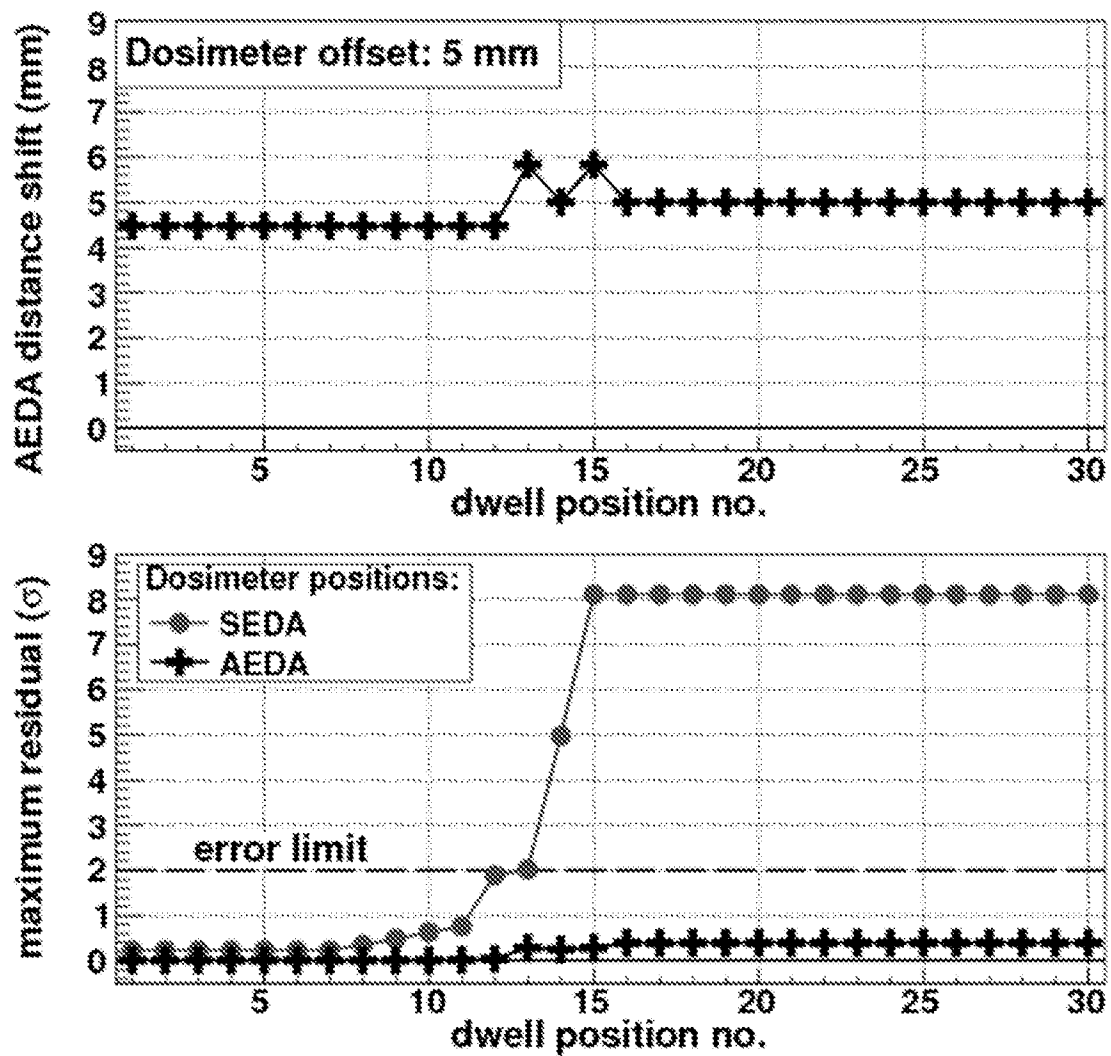


Fig. 6

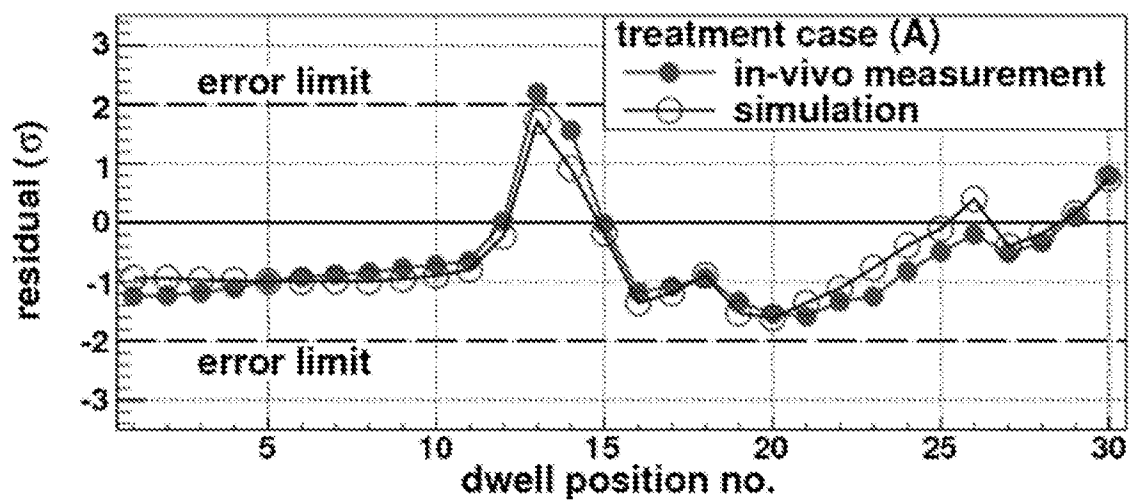


Fig. 7

INTERNATIONAL SEARCH REPORT

International application No

PCT/DK2014/050328

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61N5/10 A61B6/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61N A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/034157 A1 (SMITH RYAN LEE [AU]; FRANICH RICK DON [AU]; RMIT UNIVERSITY [AU]) 22 March 2012 (2012-03-22) page 57, line 18 - page 62, line 24 -----	1, 13
A	ANDERSEN CLAUS ET AL: "Time-resolved in vivo luminescence dosimetry for online error detection in pulsed dose-rate brachytherapy", MEDICAL PHYSICS, AIP, MELVILLE, NY, US, vol. 36, no. 11, 6 October 2009 (2009-10-06), pages 5033-5043, XP012129779, ISSN: 0094-2405, DOI: 10.1118/1.3238102 the whole document -----	1-16



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/DK2014/050328

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012034157 A1	22-03-2012	AU 2010360735 A1	04-04-2013
		US 2013303902 A1	14-11-2013
		WO 2012034157 A1	22-03-2012
