Time-resolved in vivo luminescence dosimetry for online error detection in pulsed dose-rate brachytherapy

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Purpose: The purpose of this study is to present and evaluate a dose-verification protocol for pulsed dose-rate (PDR) brachytherapy based on in vivo time-resolved (1 s time resolution) fiber-coupled luminescence dosimetry.

Methods: Five cervix cancer patients undergoing PDR brachytherapy (Varian GammaMed Plus with 192Ir) were monitored. The treatments comprised from 10 to 50 pulses (1 pulse/h) delivered by intracavitary/interstitial applicators (tandem-ring systems and/or needles). For each patient, one or two dosimetry probes were placed directly in or close to the tumor region using stainless steel or titanium needles. Each dosimeter probe consisted of a small aluminum oxide crystal attached to an optical fiber cable (1 mm outer diameter) that could guide radioluminescence (RL) and optically stimulated luminescence (OSL) from the crystal to special readout instrumentation. Positioning uncertainty and hypothetical dose-delivery errors (interchanged guide tubes or applicator movements from ±5 to ±15 mm) were simulated in software in order to assess the ability of the system to detect errors.

Results: For three of the patients, the authors found no significant differences ($P > 0.01$) for comparisons between in vivo measurements and calculated reference values at the level of dose per dwell position, dose per applicator, or total dose per pulse. The standard deviations of the dose per pulse were less than 3%, indicating a stable dose delivery and a highly stable geometry of applicators and dosimeter probes during the treatments. For the two other patients, the authors noted significant deviations for three individual pulses and for one dosimeter probe. These deviations could have been due to applicator movement during the treatment and one incorrectly positioned dosimeter probe, respectively. Computer simulations showed that the likelihood of detecting a pair of interchanged guide tubes increased by a factor of 10 or more for the considered patients when going from integrating to time-resolved dose verification. The likelihood of detecting a ±15 mm displacement error increased by a factor of 1.5 or more.

Conclusions: In vivo fiber-coupled RL/OSL dosimetry based on detectors placed in standard brachytherapy needles was demonstrated. The time-resolved dose-rate measurements were found to provide a good way to visualize the progression and stability of PDR brachytherapy dose delivery, and time-resolved dose-rate measurements provided an increased sensitivity for detection of dose-delivery errors compared with time-integrated dosimetry. © 2009 American Association of Physicists in Medicine. [DOI: 10.1118/1.3238102]

Key words: Al$_2$O$_3$:C, brachytherapy dosimetry, dose verification, $^{192}$Ir, quality assurance, uncertainty

I. INTRODUCTION

A range of quality-assurance (QA) procedures are available to assure patient safety and high quality of all parts of the brachytherapy treatment chain (i.e., everything from device commissioning to patient-specific treatment procedures). The objective of dose verification is to test that the planned dose distribution is actually correctly delivered to the patient. In vivo dose verification in remotely afterloaded intracavitary brachytherapy has typically been based on point-detector measurements in a reference point and/or a critical organ such as the rectum, bladder, or urethra. The simple ratio-
nale for this approach is that a potential dose-delivery error would manifest itself (preferably early in the treatment process) in the form of a significant deviation between measurements and plan.

In pulsed dose-rate (PDR) brachytherapy, some of the main concerns in dose delivery are errors resulting from organ or applicator movements during the treatment, applicator reconstruction mistakes, wrong applicator length, interchanged guide tubes, or afterloader malfunctions. The potential clinical consequences of such errors range from minor to serious. For remotely afterloaded brachytherapy in general, the International Commission on Radiological Protection documented that source positioning errors do happen in the clinic and that the consequence in some cases has been that the radiation was delivered outside the prescribed volume with a complete miss of the target and a risk of side effects and complications. A Japanese survey of brachytherapy accidents showed that in 224 radiotherapy facilities there were 14 potentially serious brachytherapy events between 2002 and 2004.

Certain dose-delivery errors (for example, mechanical obstruction of the source or improperly connected guide tubes) can be identified by the afterloader safety systems using, for example, built-in dummy check sources. Koedooder et al. recently analyzed afterloader error log files for 1300 treatment sessions, and concluded that PDR brachytherapy is a safe treatment modality. Not all errors can, however, presently be detected by the afterloader safety systems. Human errors such as incorrect connection of applicators to the afterloader (i.e., interchanged guide tubes) can only be detected on the basis of in vivo dosimetry. As a specific example, Mangold et al. reported that in vivo TLD was used for the identification of a transfer error involving a wrong needle length specification (15 cm in stead of 16 cm) during interstitial 192Ir brachytherapy of the breast. Without in vivo dosimetry, errors leading to overdosage of critical organs may be discovered at a late stage of the treatment due to clinical complications for the patient. In contrast, errors leading to underdosage of the target volume will reduce the change of cure, and such errors may go unnoticed. The practice for using in vivo dosimetry varies considerably among countries, and systematic use of in vivo dosimetry is often not incorporated as a standard procedure in remotely afterloaded brachytherapy.

Published studies on in vivo brachytherapy dosimetry have focused on time-integrated dose measurements using TLDs, radiophotoluminescence glass detectors, diodes, or MOSFETs. In other words, most studies have been based on the total dose per treatment session rather than, for example, the dose for individual dwell positions.

In vivo brachytherapy dosimetry to a large extent translates into knowledge of geometry and the whereabouts of the source. Nose et al. performed in vivo dosimetry in 66 patients with pelvic malignancy undergoing interstitial high dose-rate (HDR) brachytherapy. Deviations between measurements and calculated doses for the rectum and urethra were larger than 20% which was found to be attributable to independent movements of these organs and the applicators. The ability of in vivo dosimetry to actually detect errors therefore greatly depends on where the detector probes can be placed and how well these positions are known. In line with this, Nakano et al. conducted a phantom study that addressed the feasibility of dose verification directly based on estimates of HDR brachytherapy source positions derived from measurements with an array of diamond detectors placed on the surface of the skin. Time-resolved dosimetry is needed for the assessment of the dose rate for individual dwell positions. By time-resolved dosimetry, we mean that the dose rate at the point of the detector is continuously recorded second by second during the entire treatment. Tandrup et al. demonstrated the application of time-resolved dosimetry (in vivo rectal diode dosimetry) for assessment of geometrical stability of applicator and rectum positions during PDR brachytherapy of cervical cancer patients.

In vivo dosimetry may be performed in real time during remotely afterloaded brachytherapy such that the verification of measurements against planned dose can be evaluated and presented online in the brachytherapy control room. This would enable the possibility of an immediate termination of treatment in case of significant deviations. The relevance of real-time dose verification seems particularly pronounced for HDR and PDR brachytherapies since the treatment is typically delivered in a few fractions with a high dose per fraction. Furthermore, PDR brachytherapy typically requires an overall treatment time of 10–50 h per fraction, and most of the treatment is therefore carried out automatically without direct presence of hospital personnel neither in the brachytherapy control room nor with the patient. Online in vivo dosimetry in brachytherapy can be carried out using, for example, semiconductor detectors and fiber-coupled luminescence detectors based on organic scintillators, or other materials. A concern with the fiber-coupled dosimetry systems could be that optical fiber cables are difficult to handle in a clinical environment since they have a critical bending radius and should preferably not be subject to pulls or mechanical stress. The objective of the present work was to present and evaluate an online dose-verification protocol for PDR brachytherapy based on time-resolved dosimetry (1 s time resolution) using one or two point detectors placed close to or directly in the tumor region using standard brachytherapy applicator needles. The proposed protocol was evaluated on the basis of in vivo measurements for cervix cancer patients undergoing PDR brachytherapy. Furthermore, software simulations were used in a sensitivity analysis to assess if certain hypothetical errors would have been detected with the proposed protocol had they occurred during the actual treatments.

II. METHODS AND MATERIALS

II.A. Patients

In vivo measurements were undertaken for five cervix cancer patients undergoing PDR brachytherapy with a Varian GammaMed Plus afterloader and an 192Ir source (~3.7
The treatments comprised from 10 to 50 pulses (1 pulse/h) delivered by intracavitary/interstitial applicators (tandem-ring systems and/or needles). For each patient, one or two luminescence dosimeter probes (labeled A and B, respectively) were placed directly in or close to the tumor region using rigid needles (1.3 mm inner diameter) of stainless steel (patient 1) or titanium (patients 2–5). The needles were classified as being either interstitial or intracavitary needles. The interstitial needles were implanted through soft tissue into the tumor whereas the intracavitary needles were placed in the vagina with the tip anchored in the ring of modified tandem-ring applicators. The interstitial needles were only used for dosimetry in cases when these remained unloaded after the actual treatment planning. For one patient, a luminescence dosimeter probe was placed in a rectal catheter. Additional information is given in Table I including a summary of the source-to-probe distances. Figure 1 shows as an example specific details for patient 1. The positions of all applicators and dosimeters were reconstructed in the treatment planning system (TPS) (BRACHYVISION 7.5, Varian, Palo Alto, CA) on the basis of CT/MR scans acquired immediately before the treatment.

### II.B. Luminescence dosimeter system

Luminescence dosimetry was performed using an optical method involving single highly sensitive aluminum oxide crystals (Al$_2$O$_3$ :C) (Ref. 33) attached to thin optical fiber cables (1 mm outer diameter). This instrumentation and its characteristics for $^{192}$Ir dosimetry were recently described elsewhere. The purpose of the 15 m fiber cable was to guide the light between the dosimeter crystal and the remote readout instrumentation placed in the brachytherapy control room. The method uses two luminescence signals. First, so-called radioluminescence (RL) is generated spontaneously in Al$_2$O$_3$ :C during irradiation. This scintillator-like signal can be used for time-resolved monitoring of the dose delivery (1 s time resolution). Second, the crystal also acts as a passive dosimeter, and the accumulated dose for a single treatment pulse can be obtained while the dosimeter is still in the patient by optical stimulation of the Al$_2$O$_3$ :C crystal. This optically stimulated luminescence (OSL) signal is the direct optical equivalent of thermoluminescence. Light is also generated when the fiber cable itself is irradiated, and this so-called stem signal is a source of error for the RL measurements as these two signals cannot be discriminated with the present instrumentation. The OSL is not subject to this source of error as the readout takes place after the irradiations (the stem signal is a combination of Cerenkov light and fluorescence which decay at the time scale of picoseconds).

The measurements in the present study were carried out automatically during the treatments in accordance with the protocols described in Ref. 29. The alteration between the two readout modes, RL (during treatment pulses) and OSL (between treatment pulses), was triggered on the basis of an online analysis of the data. The luminescence dosimetry system was operated independently from the afterloader and the identification and aggregation of measured doses for individual applicators or dwell positions were based entirely on the time structure in the treatment plan. Due to imperfections in this procedure, dwell positions with a real-time duration of $<5$ s were not included in the dose verification based on individual dwell positions. The dosimetry system was calibrated using water phantom measurements obtained before and after the treatments. Note that within each session, the same $^{192}$Ir source was used for both calibration and patient treatments. The stem signal was measured in a water phantom set up with the $^{192}$Ir source placed approximately 10 mm from the fiber cable and 80 mm away from the dosimeter crystal. The same two reader instruments were used for all

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**Table I. Patient treatment details and information about the two luminescence probes (labeled A and B). A Martinez universal perineal interstitial template (MUPID) was used for patient 1, and the ring in modified tandem-ring applicators was used as template for needle implantation for patients 3 and 5 (Ref. 32).**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Applicators (active)</th>
<th>No. of dwell positions</th>
<th>No. of pulses</th>
<th>Luminescence dosimeter probes</th>
<th>Source-to-probe distance$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Interstitial needle</td>
<td>A (mm)</td>
</tr>
<tr>
<td>1</td>
<td>15 needles</td>
<td>52</td>
<td>50</td>
<td>Interstitial needle</td>
<td>34 (14–58)</td>
</tr>
<tr>
<td>2</td>
<td>Tandem and ring</td>
<td>26</td>
<td>10</td>
<td>None</td>
<td>26 (11–65)</td>
</tr>
<tr>
<td>3</td>
<td>Tandem and two needles</td>
<td>8</td>
<td>15</td>
<td>Intracavitary needle</td>
<td>32 (9–42)</td>
</tr>
<tr>
<td>4</td>
<td>Tandem</td>
<td>11</td>
<td>15</td>
<td>Intracavitary needle</td>
<td>29 (13–52)</td>
</tr>
<tr>
<td>5</td>
<td>Tandem and four needles</td>
<td>32</td>
<td>20</td>
<td>None</td>
<td>–</td>
</tr>
</tbody>
</table>

$^a$Dwell-time weighted mean and range (minimum–maximum).

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**Fig. 1. Patient 1 details. The left picture shows the afterloader with the $^{192}$Ir source and the 15 guide tubes used in the treatment. The two optical fiber cables for dosimeter probes A and B are guided to separate interstitial stainless steel needles inside the patient. The right picture shows a CT scan of the patient with applicators. The position of the dosimeter probes (A and B) are indicated in the picture.**
five patient measurements, but after patient 1, neutral density filters were removed from the instruments to make them more sensitive.

II.C. TPS reference doses

Reference doses were calculated for each patient in accordance with the AAPM-TG43 protocol as implemented in our own software programed in S (S-PLUS, version 7, TIBCO, Palo Alto, CA). These reference values will be referred to as TPS values. The software also predicts the progression of dose delivery second by second under consideration for the TPS values. The software was used for analyzing the impact of positioning uncertainty on TPS reference doses. It was assumed that the \(xyz\) coordinates of dwell positions and detector positions each were associated with a standard uncertainty (i.e., one standard deviation as defined elsewhere) \(u_p\) equal to 1 mm. Error propagation was carried out using a simple Monte Carlo technique: For each of the six coordinates (\(xyz\) for the source and \(xyz\) for the probe), we independently sampled random values from normal distribution functions with means equal to the plan values and standard deviations equal to \(u_p\) (i.e., 1 mm for all degrees of freedom). This procedure was repeated 1000 times for all dwell positions and resulted in distributions of possible TPS doses to the detector for every dwell position. The results were summed for each of the 1000 Monte Carlo realizations to give distributions of doses at the level of each individual applicator and subsequently for each individual patient. Standard deviations \(u_{TPS}\) of these results were calculated for all separate dwell positions, applicators, and patients.

The dose measurements were associated with a standard uncertainty called \(u_M\) which was estimated as the quadrature sum of an absolute contribution of 2 mGy (or 0.2 mGy/s for dose-rate results) and the relative standard uncertainty found in Ref. 29: Either 5% if the measurements were based on OSL results or 8% if they were based on RL results. The absolute contribution of 2 mGy originated from measured variations in the background counting rates. To illustrate the relative importance of \(u_M\) and \(u_{TPS}\) as a function of detector-source distance, we applied the above techniques in a simulation of an \(^{192}\text{Ir}\) depth-dose curve in water.

To assess the influence of the stem signal on the RL measurements, we calculated the extent to which the fiber cables were irradiated for each individual dwell position in the five treatments. Specifically, we calculated the line integral (in units of Gy cm s\(^{-1}\)) of the dose rate for 8 cm of fiber cable starting at the end of the crystal. The orientation of the fiber cables were known from the location of the applicators.

II.D. Simulated dose-delivery errors (sensitivity analysis)

Calculations were also made for a range of hypothetical errors comprising either (i) interchange of pairs of guide tubes (one pair per event) or (ii) applicator displacement errors of \(\pm 5, \pm 10,\) and \(\pm 15\) mm (one applicator and displacement distance per event). Imposing a displacement error of 5 mm (for example, as a result of a reconstruction mistake or because of a movement of the applicator during the treatment) means that all dwell positions in that applicator will be offset by 5 mm relative to the original plan coordinates. For tandems or needles, the offset is modeled to occur along the principal axis of the applicator. For rings, the offset will result in a simple rotation of all dwell positions by 5 mm within the ring.

II.E. Uncertainty analysis

The software was used for analyzing the impact of positioning uncertainty on TPS reference doses. It was assumed that the \(xyz\) coordinates of dwell positions and detector positions each were associated with a standard uncertainty (i.e., one standard deviation as defined elsewhere) \(u_p\) equal to 1 mm. Error propagation was carried out using a simple Monte Carlo technique: For each of the six coordinates (\(xyz\) for the source and \(xyz\) for the probe), we independently sampled random values from normal distribution functions with means equal to the plan values and standard deviations equal to \(u_p\) (i.e., 1 mm for all degrees of freedom). This procedure was repeated 1000 times for all dwell positions and resulted in distributions of possible TPS doses to the detector for every dwell position. The results were summed for each of the 1000 Monte Carlo realizations to give distributions of doses at the level of each individual applicator and subsequently for each individual patient. Standard deviations \(u_{TPS}\) of these results were calculated for all separate dwell positions, applicators, and patients.

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II.F. Test statistics

Given a measured dose (or dose rate) \(D_M\) for a certain dwell position, applicator or treatment pulse, and the corresponding TPS reference dose (or dose rate) \(D_{TPS}\), we define the standardized deviation \(d\) between the two values as

\[
d = \frac{D_M - D_{TPS}}{\sqrt{u_M^2 + u_{TPS}^2}},
\]

where \(u_M\) and \(u_{TPS}\) are standard uncertainties of measurements and reference values, respectively, as defined in Sec. II E. In the absence of systematic errors, we expect \(d\) to approximately follow a normal distribution function with zero mean and unity standard deviation, and we therefore define a measurement-plan deviation to be significant if \(|d| > 2.58\) corresponding to a \(P\) level of 0.01.

III. RESULTS

III.A. Positioning uncertainty calculations

Figure 2 (top panel) shows the calculated basic depth-dose curve going from 0.25 Gy at 7 mm to 5 mGy at 50 mm for a 10 s irradiation time at each depth. The middle panel in the same figure shows the relative contribution of positioning uncertainty \((u_{TPS})\) and measurement uncertainty \((u_M)\) as a function of source-to-detector distance. It is noted that positioning uncertainty dominates close to the source whereas the measurement uncertainty dominates at long distances. The figure shows that the combined uncertainty \((u_c)\) of \(u_{TPS}\) and \(u_M\) has a minimum at about 25 mm source-to-probe distance. The bottom panel shows the displacement needed to make a significant \((P=0.01)\) dose-to-plan deviation according to the test statistics described in Sec. II F. The plot shows that about 3 mm displacements can be detected close to the source whereas displacements larger than 16 mm are needed for detection at 50 mm distance.

III.B. Integrated and time-resolved results

Figure 3 shows the dose per pulse for the five patients using either OSL or RL. Generally, the dose delivery appears to have been quite stable. However, some differences from patient to patient should be noted: The results for the inter-
sternal probe in patient 5 were highly stable (0.5% relative standard deviation) whereas the rectal measurements with probe B for patient 3 were much more variable (4.6% relative standard deviation) although still random. In contrast, the measurements for patient 1, probe B included a small systematic decrease in the dose as the treatment progressed. For patient 2, we note an abrupt ~15% shift after pulse 3.

Figure 3 indicates that there was good agreement between the RL and OSL results for all five patients which is interesting since the two signals are partly subjected to different sources of errors.29 The figure also shows that there was qualitatively good agreement between measurements and TPS reference values for all cases except patient 3, probe A where all measurements were significantly lower than the TPS value. Figure 4 shows the time-resolved dose delivery during the first treatment pulse for each patient and the corresponding TPS reference profiles. The number of applicators in use for each patient can readily be identified from the plots (cf. Table I) as the measured dose rate approaches zero during an ~20 s period when the source changed from one applicator to the next. Many of the individual dwell positions can also be identified from the plots due to the change in dose rate from one position to the next. The plots show that there was qualitatively good agreement between measurements and TPS reference values for all cases except patient 3, probe A.

Fig. 2. Illustration of the relationship between uncertainty, ability to detect source displacements, and source-to-probe distance for a 10 s irradiation period with an 192Ir source identical to the one used for the treatments. The top panel shows the basic depth-dose curve going from 0.25 Gy at 7 mm to 5 mGy at 50 mm. The middle panel shows the various uncertainty components and TPS reference values and the RL measurement uncertainty, respectively. The bottom panel shows the approximate displacement distances that can be detected.

Fig. 3. Measurement results for the dose per pulse for the five patients using either RL (crosses) or OSL (circles). The mean relative standard deviations (s) are given within each panel. Within each panel, the reference TPS dose is indicated by a horizontal line and a shaded band which shows a 95% confidence interval calculated from the Monte Carlo simulations of the influence of 1 mm positioning uncertainty on the predicted TPS values.
III.C. Stem-signal calculations

The integrated fiber cable dose rate (averaged over the entire treatment) ranged from 0.002 Gy cm s\(^{-1}\) for patient 1, probe A, to less than 0.0001 Gy cm s\(^{-1}\) for patient 4, probe A. The maximum integrated fiber cable dose rate was calculated for patient 1, probe B, where one dwell position was estimated to be associated with an irradiation of 0.028 Gy cm s\(^{-1}\). It was found that approximately 1000 counts would be generated per Gy cm fiber cable exposure for the instruments used for patient 1 and approximately 4500 counts per Gy cm for the instruments used for patients 2–5. By comparison with the actual count rates, it was estimated that one dwell position was estimated to be associated with a stem signal for patient 1, probe A, and that nine dwell positions were associated with a stem signal larger than 10% for either of the two probes. All dwell positions for patient 1 with dwell times larger than 5 s were estimated to be influenced by less than 5% stem signal. The influence of the stem signal for individual dwell positions for patients 2–5 was in all cases less than 3%. The influence of the stem signal on the integral RL doses was estimated to be less than 3% for patient 1, both probes, and less than 1% for the other patients.

III.D. Dose verification

Table II shows the calculated measurement-plan discrepancies for all five patients in accordance with the statistical test described in Sec. II F. The results are given in the form of so-called error ratios \(E/T\) where \(E\) is the number of measurement-plan comparisons that deviate significantly \((P=0.01)\) and where \(T\) is the number of considered comparisons. For an error-free dose delivery, all \(E\)'s should ideally
be zero. The comparisons are organized hierarchically on the basis of (i) total dose per pulse, (ii) dose per applicator, and (iii) dose per dwell position. Comparisons are made for each individual pulse in the treatment, so the total number of applicator comparisons for patient 1, for example, amounts to 750 because there are 50 treatment pulses and 15 applicators. It can be seen from the table that the measurements for patients 1, 4, and 5 did not significantly deviate from the TPS reference values at any of the three levels of comparison (dwell position, applicator, or pulse total). In contrast, we note significant deviations for patient 3, probe A. The results with probe B for the same patient are, however, generally in agreement with the TPS reference values (the only deviations are for 3 out of 45 comparisons at the level of dose per individual applicator). For patient 2, the main deviation occurs for three of the pulses.

### III.E. Detection of simulated error events

Figure 5 shows examples of simulated error events for patient 5. The examples with interchange of two guide tubes (either guide tubes 1 and 3 or guide tubes 4 and 5) lead to a marked difference between the TPS reference profile for the correct treatment and the expected time-resolved measurements. The impact on the integrated dose per pulse is, however, marginal (4.1%) in the example involving guide tubes 4 and 5 and therefore cannot be detected using dose verification without time resolution. The example in the bottom panel of Fig. 5 with a 15 mm displacement for all dwell positions in applicator 3 leads to an ~20% change in the integrated dose per pulse and a marked change in the time-resolved measurements.

Tables III and IV summarize all simulated error events for guide tube interchanges and applicator displacements, respectively. The calculations are based on test statistics described in Sec. II F, and we classify a dose-delivery error event to be detected if at least one of the considered measurement-plan comparisons for a given patient deviates significantly ($P=0.01$ per independent comparison). The comparisons are organized hierarchically on the basis of (i) dose per pulse, (ii) dose per applicator, and (iii) dose per dwell position. The error-event detection ratio $F/S$ gives the number of detected error events ($F$) over the total number of considered error events ($S$). An ideal dose-verification system should have a detection ratio of 100%. The number of considered error events $S$ in the table can be calculated as follows: For the guide-tube error events, we note, as an example, that the treatment of patient 1 comprised 15 guide tubes which leads to 105 possible pairs of guide-tube permutations. Likewise, the number of $\pm 5$ mm applicator displacement errors for this patient amounts to $15 \times 2 = 30$ since only one applicator is considered per error event. Table III shows that the ability to detect guide-tube errors increases when we change the dose verification from integrated to time-resolved values. For probe A in patient 1, we estimate that only 5 out of 105 of the considered guide-tube permutations could be detected if based on time-integrated results whereas this ratio is 72/105 for applicator based dosimetry and 73/105 for dwell-position dosimetry. Likewise, we estimate that only 1/10 guide-tube error events would be detected for probe B.

### Table II. Dose-delivery error ratios $E/T$ for the five patients based on in vivo measurements with probe A or B and calculated TPS reference values. $E$ is the number of significant deviations ($P=0.01$) defined in relation with Eq. (1) and $T$ is the total number of considered comparisons. The error ratios are broken down by (i) dose for each patient, (ii) dose per each applicator, and (iii) dose rate for each dwell position. Only positions with dwell times longer than 5 s are included in group (iii). All error ratios are given on the basis of individual pulses. The columns “RL” and “OSL” indicate if the measurements were based on radioluminescence or optically stimulated luminescence, respectively. Probe A was not used for patients 2 and 5.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Probe</th>
<th>Full pulse</th>
<th>Applicator</th>
<th>Dwell position$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RL</td>
<td>OSL</td>
<td>RL</td>
</tr>
<tr>
<td>1</td>
<td>A</td>
<td>0/50</td>
<td>0/50</td>
<td>0/750</td>
</tr>
<tr>
<td>1</td>
<td>B</td>
<td>0/50</td>
<td>0/50</td>
<td>0/750</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>0/10</td>
<td>3/10</td>
<td>0/20</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>15/15</td>
<td>15/15</td>
<td>45/45</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
<td>0/15</td>
<td>0/15</td>
<td>3/45</td>
</tr>
<tr>
<td>4</td>
<td>A</td>
<td>0/15</td>
<td>0/15</td>
<td>0/15</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>0/15</td>
<td>0/15</td>
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</tr>
<tr>
<td>5</td>
<td>B</td>
<td>0/20</td>
<td>0/20</td>
<td>0/100</td>
</tr>
</tbody>
</table>

$^a$With dwell times $>5$ s.

### Table III. Sensitivity for detection of interchanged guide tubes. This table shows dose-delivery error ratios $F/S$ for the simulated errors where $F$ is the number of detected errors and $S$ is the number of considered error events. The error detection ratios are calculated separately for each treatment pulse, applicator, and dwell position. Patient 4 is not included in the table as this treatment only included one applicator.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Probe</th>
<th>Full pulse</th>
<th>Applicator</th>
<th>Dwell position</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>5/105</td>
<td>72/105</td>
<td>73/105</td>
</tr>
<tr>
<td>1</td>
<td>B</td>
<td>7/105</td>
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<td>B</td>
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<tr>
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<tr>
<td>5</td>
<td>B</td>
<td>1/10</td>
<td>9/10</td>
<td>10/10</td>
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</table>
patient 5 if the dose verification is based on time-integrated values versus 9/10 and 10/10 for the dose verification based on individual applicators or dwell positions, respectively. A similar trend is seen in Table IV for the detection of applicator displacement errors. For example, none of the ten cases involving ±15 mm displacements of patient 5 applicators can be detected using time-integrated dosimetry whereas this detection ratio increases to 6/10 for the applicator based dosimetry and 9/10 for the dwell-position based dosimetry.

IV. DISCUSSION

IV.A. Feasibility of fiber-coupled RL/OSL in vivo dosimetry

The study confirms the feasibility of performing in vivo luminescence radiotherapy dosimetry with aluminum oxide crystals attached to optical fiber cables as first demonstrated in in vivo OSL dosimetry for a head-and-neck cancer patient undergoing intensity modulated radiation therapy at Copenhagen University Hospital, Denmark.39 As expected from long-term laboratory tests40 and preclinical phantom measurements29 the RL/OSL dosimetry system was found to be suitable for in vivo 192Ir brachytherapy dosimetry from the perspective of measurement uncertainty and sensitivity. The overall main feature of the system was the ability of the 1 mm dosimeter probes to fit into standard guide tubes and applicators. We are not aware of published works that directly present in vivo time-resolved dose verification on the basis of measurement from standard applicators used in remotely afterloaded brachytherapy.

IV.B. Dose-verification outcome

The concept of dose-verification explored in this work is based on a direct comparison of in vivo point measurements and TPS values at the position(s) of the dosimeter(s). Generally the in vivo measurements agreed well with the calculated TPS reference values as shown in Figs. 3 and 4 and Table II. The agreement concerned dwell times, dose-rate patterns, dose per pulse for individual dwell positions, applicators and patients, and the results indicated a stable dose delivery in most cases. The main measurement-plan discrepancy was for patient 3, probe A. This deviation is believed to have been caused by a gross error on the position of the dosimeter probe. The probe was probably not correctly inserted into its intercavitary needle and the measured dose rate indicates that the crystal was placed about 35 mm from the assumed position at the bottom of the needle channel. It should be pointed out that the other probe for that patient (probe B) gave results in good agreement with the TPS reference values. These measurements were carried out before the software was able to procedure online measurement-plan comparisons, so no extra effort was made to clarify the origin of this discrepancy during the actual treatment. Likewise, the reason for the discrepancy of the initial three pulses for patient 2, probe B remains unknown. For patients 1, 4, and 5, no significant measurement-plan deviations were observed for neither probe A nor probe B.

IV.C. Time-resolved versus integral dose verification

The RL signal provided measurements of the dose delivery with a time resolution of 1 s, and these measurements could therefore be used to assess the dose for each dwell position, applicator, or pulse total which in turn could be compared with the corresponding TPS reference values. The results in Tables III and IV showed that the estimated ability to detect error events increased with improvements in time resolution. For example, we could estimate that less than 5% of the considered guide-tube errors for patient 1 would be obtained with TLDs whereas the estimated error-event detection ratio was about 70% with time-resolved dose verification even at the level of just knowing the dose delivered for each applicator.

The increased ability to detect errors with time-resolved dose verification is simple: The relative importance of, for example, a displacement of a given applicator will be larger if the dose for that particular applicator can be considered in isolation from other parts of the plan. Likewise for the considered guide-tube errors, the extra integrated dose received from one applicator could be partly balanced by a similar decrease in integral dose from another guide tube (see middle panel in Fig. 5).

Table IV. Sensitivity for detection of applicator displacements of ±5, ±10, and ±15 mm. This table shows dose-delivery error ratios F/S for the simulated errors where F is the number of detected errors and S is the number of considered error events. The error detection ratios are calculated separately for each treatment pulse, applicator, and dwell position.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Probe</th>
<th>Full pulse</th>
<th>Applicator</th>
<th>Dwell position</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>±5 mm</td>
<td>±10 mm</td>
<td>±15 mm</td>
</tr>
<tr>
<td>1</td>
<td>A</td>
<td>0/30</td>
<td>0/30</td>
<td>0/30</td>
</tr>
<tr>
<td>1</td>
<td>B</td>
<td>1/30</td>
<td>2/30</td>
<td>2/30</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
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</table>
It should be pointed out that the present study addresses the use of independent point detectors. The above conclusion in favor of time-resolved dosimetry does not imply that the best overall dose verification (i.e., the one that will help identify only the real problems) is achieved in this way. The use of integral dosimetry with, for example, a stack of TLDs (Ref. 10) or a linear array of semiconductors provides an improvement in spatial resolution which may be better than using one or two independent point detectors with time resolution. The study only suggests that on a detector-by-detector basis, time-resolved dose verification is always to be preferred whenever possible.

It is relatively easy to calculate integral doses for each pulse and applicator (due to the long delay between these) whereas the dose rate for given dwell positions are more difficult to extract. The latter problem is caused by the lack of any communication link between afterloader and dose-verification system which on the other hand could be viewed as an important feature as it would otherwise compromise the independence of the dose verification.

IV.D. Where to perform the measurements

The particularly good agreement between measurements and TPS reference values for patients 1 and 5 could suggest that measurements in interstitial needles are to be preferred whenever possible. For treatments that anyway involve a large number of needles and long treatment times (such as the 50 h treatment of patient 1), it may be justified to insert one or two additional interstitial needles just for the purpose of in vivo dosimetry.

The proposed simple formalism for dose verification (Sec. II F) explicitly requires detailed knowledge of the uncertainties for both TPS reference values (utPS) and measured doses or dose rates (utD). Figure 2 (bottom panel) illustrated that from the perspective of error detection, it is optimal to be as close to the source as possible. The data in Table I therefore suggest that probe B for patient 5 was probably the best placed probe for dose verification as it on the average was only 22 mm away from the source (range of 10–45 mm) whereas the rectal probe for patient 3 (probe B) was in the worst position as this probe on the average was 41 mm away (range of 26–53 mm). The technique for fixation of the fiber probes at the bottom of applicator needles could probably be improved, and in at least one case (patient 3, probe A as already discussed) it appears that one dosimeter probe was not correctly positioned within the applicator.

IV.E. Measurement uncertainty

Assuming that the five patients were indeed administered the correct treatment, then Table II indicates to what degree the proposed in vivo dose-verification protocol will generate false alarms. From the selected significance level for error detection (P=0.01) we a priori would expect that about 1% of all comparisons would by random result in significant measurement-plan deviations. The error ratios in Table II are, however, generally much lower. For example, none of the 1300 dwell-position comparisons for patient 1, probe A resulted in significant deviations. The reason for the discrepancy could be that the involved uncertainties are not independent. If, for example, the basic calibration of the detector system is off by 10% in one comparison, then it will also be so in the next one. The 1% rate of false alarms is the expected random error rate for any given comparison if repeated many times for different treatment sessions and with a recalibrated dosimetry system each time. Another reason for the low error ratios could be that the assumed uncertainties were set too high. An improved uncertainty model could include nonisotropic positioning uncertainty rather than the 1 mm uncertainty for all degrees of freedom applied here.

Table IV showed that only few of the simulated applicator displacement errors could be detected for patient 1. This was due to the low doses per applicator (less than 10 mGy for most applicators) and dwell positions. Such low-level measurements are subject to a relatively large uncertainty contribution from variations of the background counting statistics as illustrated by Fig. 2.

The good agreement between RL and OSL integral doses in Fig. 3 shows that the RL signal was not substantially polluted by the so-called stem signal (see Sec. II B) for any of the five patients. From the calculated exposure of fiber cable during the treatments it was estimated that the stem signal affected the time-resolved RL dosimetry at any of the dwell positions by less than 3% for patients 2–5. For patient 1, however, we did assess that nine dwell positions could have been affected by 10%–30%. The dwell times for these nine dwell positions were less than 5 s, and they were therefore not included in the dose verification shown in Table II. The study shows that it remains relevant to reduce the stem effect for the present instrumentation as discussed elsewhere. It could also be of relevance to adapt a treatment-plan based model of measurement uncertainty to account not only for the potential influence of the stem effect but also for angular response and detector energy dependence (i.e., detector-source distance).

IV.F. Practical aspects of online dose verification in a clinical setting

The prototype system (software and hardware) developed during this study can essentially automatically record, analyze, and visualize the data online during an actual radiotherapy session. Ultimately, we imagine that such a system could be used routinely for dose verification during PDR treatments as follows: After the treatment planning and the initiation of the plan, the radiophysi est would monitor that the first pulse of the PDR brachytherapy is delivered with good agreement between TPS predictions and in vivo measurements. This would be the prime dose verification. The objective of measurements during subsequent treatment pulses would primarily be to check the stability of the dose delivery. Graphical visualization similar to Figs. 3 and 4 would probably be highly useful for the radiophysi est in the process of resolving the reason for any measurement-plan deviations and in the subsequent decision making. Although this study demonstrates certain potentially beneficial features
of the suggested protocol, it should be stressed that in vivo dosimetry is associated with a certain work load which may or may not be justified given available resources and the actual risk of errors.

V. CONCLUSIONS

It has been demonstrated that it is feasible to conduct online time-resolved in vivo dosimetry using the RL/OSL signals from fiber-coupled Al2O3:C probes placed in standard brachytherapy stainless steel/titanium needles. Time-resolved measurements were found to provide a good way to visualize the progression and stability of the treatments.

For three of the patients, we found no significant differences ($P > 0.01$) for comparisons between in vivo measurements and calculated reference values at the level of dose per dwell position, dose per applicator, or total dose per pulse. For the two other patients, we noted significant deviations for three individual pulses and for one dosimeter probe. These deviations could have been due to applicator movement during the treatment and one incorrectly positioned dosimeter probe, respectively.

Computer simulations showed that the likelihood of detecting a pair of interchanged guide tubes increased by a factor of 10 or more for the considered patients when going from integrating to time-resolved dose verification. The likelihood of detecting a pair of interchanged guide tubes increased if the average source-to-probe distance was small.

ACKNOWLEDGMENTS

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