Project title: Improving Patient Safety Through Online Treatment Monitoring in Brachytherapy

Academic title and name: MSc., Erik Buch Jørgensen

Introduction

Treatment verification is an essential part of radiotherapy to prevent wrong delivery of the dose. While verification with the patient in treatment position is a standard procedure in external beam radiotherapy, it is rarely performed during brachytherapy (BT) as there is lack of adequate and commercially available equipment. BT is the delivery of ionising radiation by small radioactive sources placed inside or close to the tumour. While BT delivers very focal treatment with excellent clinical results, there is currently an urgent need to improve the patient safety through improved treatment verification. The most direct way of treatment verification is to measure the delivered dose in the patient during treatment - known as in vivo dosimetry (IVD). Current IVD in BT are inaccurate and have shown deviations of more than 30% [1]. Furthermore, current dosimeters only provide post-treatment feedback and can only register errors rather than prevent them.

The need for monitoring of BT has become more evident over the last decade with multiple reports of incidences [2-4]. Two surveys made by GEC-ESTRO (Groupe Européen de Curiethérapie - European Society of Radiotherapy and Oncology) in 2013 and 2016 have shown that 83% of the clinics had encountered errors during BT. Less than 10% of the responders performed IVD, while more than 90% were interested in implementing and performing real-time dosimetry if an appropriate system had been available [5,6].

This PhD study will address the need for improved patient safety in BT, by bringing a research system from prototype and into clinical practice with the long term aim to make value for patients by facilitating commercialisation of the research system. The project is inter-disciplinary and branches from engineering, medical physics and to clinical medicine. Project partners include School of Engineering (software developments), Faculty of Science and Technology (dosimetry laboratory), Aarhus University Hospital (clinical developments and testing), an industrial partner – Elekta (potential commercialisation), and international research partners (technological developments and clinical testing).

In vivo dosimetry at Aarhus University Hospital

AUH together with MD Anderson Cancer Center (MDACC), Houston, USA, and the Technical University of Denmark (DTU) have developed an IVD system (fig. 1) for online monitoring in BT [7-11]. The dosimeters are small crystals that are placed inside the tumour through a BT catheter. The crystals are assembled in a laboratory at Institute of Science and Technology, AU. The crystals are read out continuously throughout the treatment and provide information about dose inside the tumour. The system is easily adaptable in a treatment workflow (fig. 2) and is currently being tested clinically at AUH (>30 prostate and >10 gynaecological cancer treatments). Systems with similar performance are currently experimentally available in 4 universities worldwide, and AUH is in a unique position as the only site having experience with application in patients.

A post-treatment analysis of patient measurements at AUH [11] shows that dose rate information can be used to derive the actual position of the source (source tracking). Accurate source tracking is extremely important as the majority of events in BT are caused by a misplacement of the source, and source tracking gives therefore a direct indication if the treatment does not progress as intended. With our current methodology, a source misplacement can be identified within 10 s. The applicant has during his master project shown that over and under dosage to tumour and organs can be determined based on the source tracking information, hence guiding the clinical staff to judge if deviations are

clinically relevant [12]. The next step is to bring the retrospective methodology into prospective clinical use.

Overall Aim of the PhD study:

The overall aim of the project is to demonstrate that online monitoring is possible in BT. The online monitoring tool will provide clinically relevant information to the clinical staff during treatment, to aid them in real-time identification and interruption of treatment in case of misadministrations. The overall aim will be addressed through:

- Realising a source tracking accuracy of <1mm.
- Propagating source tracking into online reconstruction of dose.
- Multi-centric study of online monitoring in prostate and gynaecological BT.

Part 1: Accuracy of the dosimetry system

Background:

The IVD system has been thoroughly characterised [7]. However, an investigation on 15 patient measurements performed by the applicant showed deviations in source positions measurements from MR-images to source tracking. These deviations must be understood in order to provide accurate information to the clinicians.

Aim

To ensure that the system provides positional information with accuracy of <1 mm.

Hypotheses:

- The deviation can be understood through a comparison between in vivo and in vitro measurements.
- Given that the deviations can be accounted for, the online monitoring system will reach an uncertainty < 1 mm for source tracking.

Material and methods:

The investigation will contain three parts.

1) In vitro measurements. Patient treatments will be simulated by placing BT needles in a phantom in a realistic configuration. The data from the actual treatment will be compared to the in vitro measurements.

2) Analysis of 30 treatments performed at AUH: Two MR scans was acquired before each treatment and a third MR scan was perform after. The source tracking will be compared with the MR-images. If the deviations are present in phantom measurements, steps can be taken to reproduce and isolate the cause of the deviations. If not, an explanation must be found in the differences from phantom measurements to patient measurements.

3) A stay in the group of prof. Luc Beaulieu at Université Laval, Quebec, Canada. The group is one of the leaders within source tracking and Monte Carlo dosimetry. Laval is one of the four other institutes with a similar dosimetry system. The source tracking developed at AUH will be tested against systems at Laval. Monte Carlo simulations will be used to understand and substantiate all experimental results.

Feasibility:

Data from the 30 patient measurements will provide a clear indication of the accuracy of the system. An agreement for the research stay in Laval has been made.

Perspectives:

A 1 mm uncertainty would enable identification of more than 70% of all misadministrations in BT.

Part 2: Dosimetric feedback based on source tracking

Background:

Once the accuracy of source tracking has been optimised, the effect of any offsets can be investigated. This investigation will ensure that the clinical staff only reacts on clinically relevant deviations. A methodology for retrospective transformation of source tracking data into evaluation of the 3D dose distribution was developed by the applicant as part of his master's project [12].

Aim:

To evaluate the dosimetric effects of source offsets in a BT treatment

To determine error detection criteria and required action in case of deviations during a treatment.

Hypotheses:

- The actual delivered dose to tumour and organs can be established with <4% uncertainty.
- An error decision tree can be designed based on feedback of reconstructed dose distributions.

Material and methods:

A three month stay at Elekta (the largest BT vendor in the world) will facilitate a comparison of the dose calculation engine against their commercial system. During the stay, the applicant will be taught in methods on how to benchmark and optimise a dose calculation system to the standard of international clinical use.

The dose distribution will be reconstructed for 40 treatments and the planned and delivered treatment compared. Medical doctors (MDs) from AUH will guide the applicant in evaluating the severity of deviations between planned and delivered dose. To broaden the scope of this analysis, simulation with provoked errors will be performed as well.

Feasibility:

A dataset from 40 treatments is sufficiently large to identify the effect of small fluctuations. The effect of gross errors can be simulated by artificially adding shift to individual needles. Elekta has agreed to host the applicant for a 3 month stay.

Perspectives:

The possibility to reconstruct the full dose distribution based on measurements from a single dosimeter will strengthen the value of IVD and opens up for new opportunities in the utilisation of online monitoring.

Part 3: Clinical feasibility of online monitoring

Background:

The last part of this project will bring online versions of the system to multiple clinics. This step will test the robustness of the system, provide clinical data for future investigations, and finally bring awareness to clinics and the research community that IVD is possible, bringing highly relevant information at a low cost and a small additional work load.

Aim:

To transform the retrospective analysis in to an online monitoring system and test it in various clinical scenarios.

Hypotheses:

- The delivered dose to tumour and organs at risk can be obtained within 10s calculation time.
- The multi-centre study is sufficiently large to evaluate the robustness of the system and contain misadministrations and near-misses.

Material and methods:
A new user interface for the system will be developed by three students from School of Engineering (SE), Aarhus University with the applicant as co-supervisor. The MDs at AUH will advise the applicant in choosing clinically relevant information based on their experience using the system at AUH. After a successful implementation at AUH, two Danish (Odense University Hospital and Rigshospitalet) an two international (MDCC and Laval) institutes will follow. Dissemination of the system to the additional centres will be carried out by post doc Johansen, J. while the applicant will analyse the in vivo data obtained from the clinics.
Feasibility:
Agreements have been made with all institutions involved in the multi-centre clinical study and the required funding is secured. The three students from SE have already begun the development of the interface.
Perspectives:
Proof that online monitoring in BT is possible will increase the awareness in the community. AUH will be at the forefront of this, and the tested system has the potential to become a commercial product.

The research group:
The applicant Msc Erik Buch Jørgensen will perform all parts of the project under the supervision of Prof. K. Tanderup (main), who is ranked as a top-ten expert in BT [13], two post docs, who will be in charge of the daily supervision and two MDs, one for prostate (S. Buus) and one for gynaecological (P. Petric) who will introduce and supervise the applicant in parts of the project related to the clinic. Three bachelor students from SE will also be involved in the project.

Impact
An operational verification system will open for a new level of patient safety in BT in two ways:
1) The individual patient will benefit from immediate action in case of misadministration.
2) The community will benefit from enhanced knowledge on the spectrum of errors in BT, which can be used to improve the BT procedures. Studies have shown the importance of registering both errors and near misses to improve the treatment form [14]. Patients treated with BT in Denmark will directly benefit from this study. The three main BT institutions in Denmark are involved in this project and will get an IVD system implemented during the next three years. This implementation is currently supported both by the Novo Nordisk foundation (2MDKK) and the Danish Comprehensive Cancer Center (165.000DKK). A plan to expand the multi-centre study is planned after this project. More than 5 additional institutes have already indicated their interest. Leadership of a multi-institutional clinical study will strengthen AUHs international, and it will give Danish institutes a direct connection to recent findings.

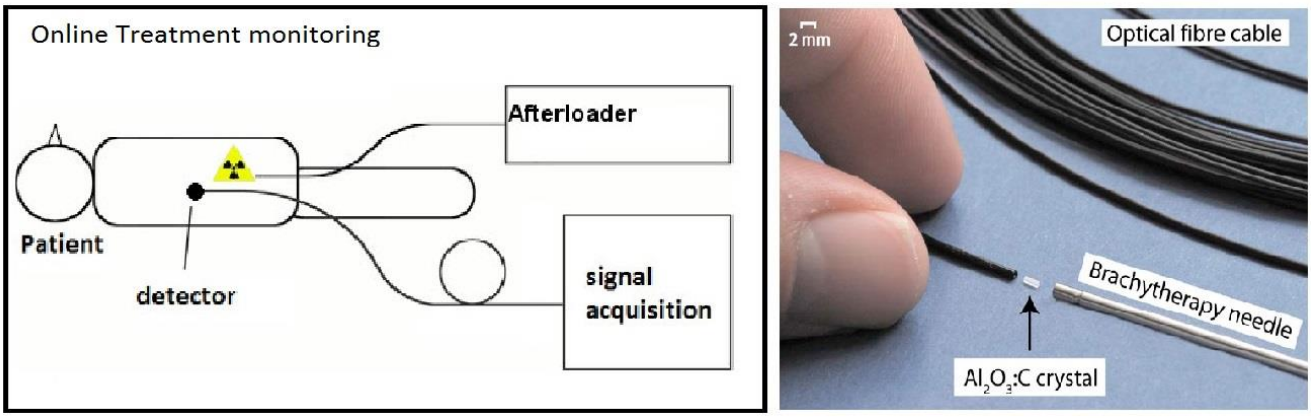

Figure 1: To the left: Basic setup of the system monitoring a patient treatment. To the right: An exploded view of the dosimeter used at AUH: A radioloumiscent crystal and optical fiber which fits inside a standard BT catheter.

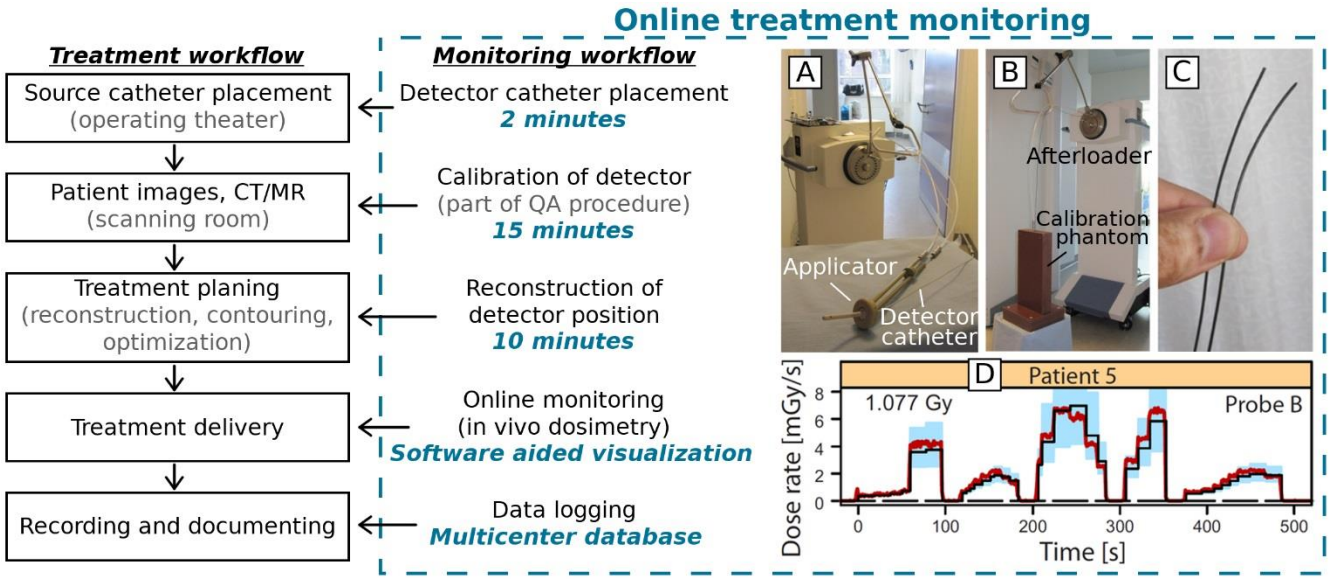

Figure 2: Treatment and monitoring workflow. A) Gynecological brachytherapy applicator. B) Calibration phantom and afterloader. C) Two dosimeter probes. D) Dose rate against time plot for the planned treatment and delivered (dosimeter measurements) treatment.

References

1 Tanderup K, Beddar S, Andersen CE, Kertzscher G, Cygler JE. In vivo dosimetry in brachytherapy. Med Phys. 2013 Jul;40(7):070902

2 UK GOV, Radiotherapy Errors and Near Misses Data Report, URL: https://www.gov.uk/government/publications/radiotherapy-errors-and-near-misses-data-report (Acessed 14/9/2018)

3 Ganesh T. Wrong brachytherapy treatment delivery in 100 patients. J Med Phys 2014;39:129

4 Bogdanich W. At V.A. Hospital, a Rogue Cancer Unit, New York Times 2009, June 20.

5 Spasic E. Private communication

6 Braphyqs & GEC-ESTRO Seminar on On-Line Treatment Verification. Brussels, Belgium. 2014. [cited August 30 2017]. Available from: http://www.estro.org/about/governance-organisation/committees-activities/gec-estro-in-vivo-dosimetry-seminar

7 Andersen CE, Nielsen SK, Lindegaard JC, Tanderup K. Time-resolved in vivo luminescence dosimetry for online error detection in pulsed dose-rate brachytherapy. Med Phys. 2009 Nov;36(11):5033-43.

8 Andersen CE, Nielsen SK, Greilich S, Helt-Hansen J, Lindegaard JC, Tanderup K. Characterization of a fiber-coupled Al 2 O 3:C luminescence dosimetry system for online in vivo dose verification during I 192 r brachytherapy.

9 Kertzscher G, Andersen CE, Siebert FA, Nielsen SK, Lindegaard JC, Tanderup K. Identifying afterloading PDR and HDR brachytherapy errors using real-time fiber-coupled Al(2)O(3):C dosimetry and a novel statistical error decision criterion. Radiother Oncol; 100(3):456-62, 2011

10 Kertzscher G, Andersen CE and Tanderup K. Adaptive error detection for HDR/PDR brachytherapy: Guidance for decision making during real-time in vivo point dosimetry. Med. Phys. 2014; 41:052102

11 Johansen J, Rylander S,Buus S, Bentzen L, Hokland SB, Søndergaard CS, With AKM, Kertzscher G, Tanderup K. Time-resolved in vivo dosimetry for source tracking in brachytherapy. Brachytherapy 2017 (Accepted for publication)

12 E. B, Jørgensen, Dosimetric impact of needle movements in HDR-BT treatments of the prostate. Jan 2018 (Available at the Library, Institute of physics and Astronomy, Aarhus University)

13 expertscape.com/ex/brachytherapy

14 Brenda G. Clark et al., The management of radiation treatment error through incident learning, Rad. and Onc. 2010, 95;344-349