# Novel in-treatment dose verification methods for adaptive radiotherapy

# Valorization

## Background and target groups of portal dosimetry

Cancer is one of the main causes of death worldwide. Radiotherapy is one of the three treatment modalities available (*i.e.* Surgery, chemotherapy, radiotherapy) and radiotherapy is applied in approximately 50% of all cancer patients. In-treatment dose verification of radiotherapy is essential to assure treatment quality and document the treatment delivery and it facilitates adaptive radiotherapy.

The main aim of radiotherapy is to deliver the planned or desired dose. During the course of treatment there are many potential uncertainties and causes of dose differences. The uncertainties and causes can be subdivided in four categories: 1) Errors in data transfer to the treatment equipment; 2) Errors caused by technical failures of the treatment machine (*i.e.* stuck MLC leaf); 3) Inaccuracies during the treatment planning process and, 4) Patient setup and geometry changes. Accurate dose delivery is essential because a small difference in dose of approximately 5% to the target can modify treatment outcome or increase the risk to severe side effects drastically.

Dosimetry and especially in-treatment dosimetry is a method for verifying the treatment quality in a quantitative way. While pre-treatment or plan quality assurance many methods exist to verify treatments, for in-treatment verification especially of highly dynamic treatments the methods are much more limited. For in-treatment dosimetry several detectors can be used: 1) Thermoluminescent dosimeters (TLDs); 2) Optically stimulated luminescent dosimeters (OSLDs); 3) Radiophotoluminescent dosimeters (RPLDs); 3) Film-radiographic and radiochromic; 4) Metal-oxide semiconductor field effect transistors (MOSFETs); 5) Plastic scintillation detectors, and 6) Electronic portal imaging devices (EPIDs). The disadvantage of most detectors (*i.e.* TLD, OSLD, RPLD and MOSFET) is that only point doses can be measured while film and EPID dosimetry can measure a planar dose. Another disadvantage of many detectors is that the can only be analysed after the treatment (*i.e.* TLD, OSLD, RPLD and film). The EPID however has been shown capable of acting as a planar dosimeter that can measure the dose during the treatment itself and can be both analysed during the actual delivery and after the treatment. Portal dosimetry has the advantage that besides planar portal dosimetry other methods have been developed for in-treatment dose verification to 3D portal dosimetry and time-resolved portal dosimetry. These methods have been developed at out institute.

In-treatment portal dosimetry is gaining interest and is even mandatory to apply in several countries across Europe (*i.e.* Denmark, France and the United Kingdom) due to serious radiotherapy accidents. Although these accidents are rare and radiotherapy is one of the safest cancer treatments, in-treatment dose verification not only verifies technically accurate delivery but also verifies relevant patient related changes that can be captured and acted upon. Portal dosimetry can be used to assure treatment quality, document the treatment delivery and facilitates adaptive radiotherapy. In this thesis we have shown that portal dosimetry is a valuable method especially for radiotherapy and is essential for the treatment quality. Portal dosimetry reaches it highest potential when applied to patients with a high risk of anatomical changes throughout the delivery of the treatment. While each patient could benefit from in-treatment portal dosimetry, this technique can be applied on most linear accelerators because the EPID is installed on nearly every machine. Both the large number of patients benefitting from portal dosimetry and the high availability of EPIDs in radiotherapy departments creates a large basis for a commercial solution of portal dosimetry to be integrated in the daily clinical practice of the radiotherapy departments, as is mandatory in several European countries.

## Background and target groups of portal dosimetry

To successfully commercialize portal dosimetry with the current absolute dose under full-scatter conditions measured with the EPID a complete integration in the clinical radiotherapy workflow is necessary. The the algorithms, methods and knowledge used and developed for 2D portal dosimetry at our institute have been licensed to one of the largest equipment suppliers in radiotherapy (VARIAN Medical Systems) and some methods have been patented in collaboration with the same company.

Furthermore, gross dose delivery errors should be captured with an "on-line" or "real-time" dose delivery verification method based on time-resolved portal dosimetry methods. While for the subtler dose delivery differences planar portal dosimetry (both time-integrated as time-resolved) and 3D portal dosimetry results should be automatically generated and analysed for "off-line" presentation and review. However, to minimize clinical workload the "off-line" review of presented portal dosimetry results automated methods should be created to select treatments to present to the end-user to review while the remaining treatments should be automatically archived in the patient electronic medical record for treatment documentation purposes. Decision criteria to trigger alerts and actions are therefore necessary to optimize large scale clinical applicability.

Besides a portal dosimetry product that can be used with any linear accelerator the required knowledge of reviewing and analysing is essential for the decision-making for adaptive radiotherapy. This "expert" knowledge and the analysis of portal dosimetry methods can be commercialized as a service to radiotherapy departments to improve their clinical guidelines and protocols when using portal dosimetry.

Besides a portal dosimetry solution and "expert" knowledge consultancy, the main hypothesis of this thesis is that portal dosimetry information acquired in-treatment is useful for informed decision making for adaptive radiotherapy. This was definitely shown, but needs to

be further explored in the next few years. The aim of such an exploration is to define adaptive radiotherapy decision protocols. The protocols should standardize treatment adaption decision to improve treatment accuracy. The improved treatment accuracy should minimize side-effects and optimize local tumour control.

## Innovation in comparison to other products in the market

Currently most solutions offered to apply patient specific plan quality assurance are applied with specialized hardware. Solutions like the octavius (PTW, Freiburg, Germany), Matrixx (IBA, Schwarzenbruck, Germany), Delta$^4$ (Scandidos, Uppsala, Sweden), MapCHECK (Sun Nuclear, Melbourne, United States) only offer pre-treatment patient specific quality assurance. Usage of these hardware solutions is also time-consuming because in most cases the device and phantom has to be set-up in the treatment room before the measurement. Next to this a special quality assurance plan needs to be created to compare measured versus predicted dose. This occurs in many cases in the treatment planning system and this is exported in order to be able to compare results in specialized software. Creating a special quality assurance plan is not necessary when using pre-treatment quality assurance with the portal dosimeter and no special phantoms need to be set-up for the measurement. Portal dosimetry therefore can be a fast and accurate substitute to these dedicated devices for patient specific plan quality assurance. Besides the pre-treatment portal dosimetry, it has been shown that portal dosimetry is as an adequate procedure for in-treatment dose verification. Portal pre-treatment dosimetry is already commercially available and supplied by multiple different vendors. The solutions from Varian medical systems (PortalVision), EPIdos (EPIQA) and Standard Imaging / Math Resolutions (DosimetryCHECK) only offer patient specific plan quality assurance or pre-treatment portal dosimetry. The only portal dosimetry solution also able to apply in-treatment portal dosimetry is the solution from DOSIsoft (EPIgray).

Table 1 shows an overview of the solutions currently commercialy available and our solution. It should be noted that many of the algorithms, methods and knowledge used and developed at our institute have been licensed to one of the largest equipment suppliers in radiotherapy and some methods have been patented in collaboration with the same company. The time-resolved portal dosimetry methods developed at our institute received a prestigious international award (Jack Fowler award, ESTRO). One of the major advantages of the methods developed at our institute is that it is based on absolute portal dosimetry. The methods are developed for each type of verification from integrated planar portal dosimetry to time-resolved 4D portal dosimetry. Next to this the methods can be modularly used for each type of photon-based treatment modality from 3D CRT to FFF beam VMAT treatments. None of the commercially available solutions offer this completeness with the different types of verifications possibilities.

Table 1: The different commercially available solutions in compared to each other.

| Product | Hardware solutions | Radiographic film | Commercial portal dosimetry | MAASTRO portal dosimetry |
|---|---|---|---|---|
| | 1) Delta[4]<br>2) Octavius<br>3) Matrixx<br>4) MapCHECK | EBT[3] | 1) PortalVision<br>2) EPIGray<br>3) EPIDos<br>4) Dosime-tryCHECK | |
| **Company(s)** | 1) Scandidos<br>2) PTW<br>3) IBA<br>4) Sun Nuclear | Gafchromic | 1) Varian Medical Systems<br>2) Dosisoft<br>3) EPIQA<br>4) Standard Imaging / Math Resolutions | |
| **Detector** | 1) Ionization chamber<br>2) Ionization chamber<br>3) Ionization chamber<br>4) Diodes | Film | EPID | EPID |
| **Pre-treatment** | 2D-3D | 2D | 2D-3D | 2D-3D time integrated and time-resolved |
| **In-treatment** | No | Yes | Yes, EPIGray only | Yes |
| **Measurement time (pre-treatment / in-treatment)** | - / N/A | +/- / +/- | + / + (EPIGray) | ++ / ++ (fully automated) |
| **Accuracy** | ++ | ++ | + / - | + |
| **Cost** | +/ - | - | ++ | ++ |

## Planning and realization of portal dosimetry to daily clinical practice

The used methods for integrated planar and 3D portal dosimetry will be integrated in a commercial solution to be released in the next 2 to 4 years and can be used in clinics across the world. For the time-resolved methods used in this thesis the methods are already patented (Patent No: 14/074,144 pending) by the same company and Maastro Clinic and these methods might become available after a successful introduction of the current time-integrated transit planar dosimetry and time-integrated 3D portal dosimetry solution. This means that time-resolved portal dosimetry will be available within the next decade.

Besides the development of more accurate models and other technical innovations, clin-

ical decision protocols for adaptive radiotherapy should be developed now. These decision protocols should eventually result in national and international guidelines to accurate and adequate use of portal dosimetry in daily clinical practice. At this moment for an European research project ARTFORCE (ClinicalTrials.gov Identifier: NCT01504815) the portal dosimetry solution is implemented by us in several different sites across Europe. One of the aims of this project is to investigate the predictive power of portal dosimetry and the added benefit in daily clinical practice for adaptive radiotherapy. Next to this portal dosimetry is used within this trial to document the actual treatment delivery. While the ARTFORCE trial documents the treatment and defines decision protocols based on daily in-treatment measurements also in silico studies or trials should be performed. The in silico studies or trials should investigate in a controlled environment the behaviour and sensitivity and specificity of the different in-treatment portal dosimetry methods which can be used. The in silico results can then be validated in a trial like the ARTFORCE study. The knowledge acquired by the in silico trials and portal dosimetry in general could be commercialized as a service for training and advice. Such a service could be offered immediately after the introduction of the commercial product.

## Conclusion

Portal dosimetry and especially in-treatment portal dosimetry is subject to commercial interest by both vendors and radiotherapy departments across the world but especially in Europe. In-treatment portal dosimetry will enable the identification of dose differences caused by several different sources but especially patient specific differences in patient setup, and changes in patient anatomy. To quote Mijnheer et al "All treatments with curative intent should be verified through in treatment dose measurements in combination with pre-treatment checks". The interest in portal dosimetry and new legislations in especially Europe has led to the licensing of the current portal dosimetry methods, and that novel time-resolved portal dosimetry methods have been patented in collaboration with a large medical company and might become commercially available in the next few years. Especially the novel time-resolved portal dosimetry can play an essential role in the in-treatment verification of highly dynamic treatments like volumetric modulated arc therapy. While the methods are being implemented for large-scale future use the adaptive strategies have to be developed as they have been developed up to now based on image guidance, which should now be extended to dose guidance.