Quantitative methods for improved error detection in dose-guided radiotherapy

Valorization Addendum

Relevance

Cancer has been and will remain a prominent disease worldwide. Over the years, treatment options have improved substantially and quickly. In the field of radiotherapy, technological advancements have driven the development of more conformal, but also more complex treatment. These advancements have intensified the need for accurate treatment verification, such that treatment errors can be detected and corrected, avoiding potential ineffective treatment or harm to patients. Additionally, *in vivo* error detection methods can be employed for adaptive radiotherapy, in which a patient's treatment plan is adjusted when persisting errors occur, personalizing radiotherapy treatment even further. In several countries, *in vivo* verification of the treatment has even become mandatory.

Portal dosimetry using the electronic portal imaging device (EPID) has proven to be a suitable and flexible candidate for verification of complex treatments. It can be used in different stages of the radiotherapy workflow (i.e., pre-treatment and *in vivo*) as well as provide dose distributions in various dimensions (i.e., 2D, 2D+time, 3D and 4D), which is necessary for increasingly complex treatments. Using portal dosimetry, the true dose received by the patient can be recorded. With the addition of the methods described in this thesis, portal dosimetry can become an even more effective method for verifying radiotherapy treatment and detecting errors, thereby improving overall patient treatment.

Products, innovation and target groups

Over the years, multiple vendors have invested in the development of EPID-based portal dosimetry systems. This resulted in commercially available systems with different capabilities, ranging from point dose verification (e.g., SOFTDISO (Best Medical, Italy)), to 2D (e.g., SunCHECK (Sun Nuclear, Melbourne, FL, USA)) and 3D dose verification (e.g., Dosimetry Check (LifeLine Software, Inc., Austin, TX, USA)) or a combination thereof (e.g., 2D and 3D with iViewDose (Elekta, Stockholm, Sweden)). None of these solutions currently offer time-resolved dose verification. The big advantage of the EPID is that it is widely available as it comes with most linacs, hence, no additional hardware is needed. Nevertheless, the EPID was not originally designed for dosimetry, which necessitates calibration and complex models for acquiring dose distributions, which the aforementioned software packages facilitate.

A general issue that vendors of portal dosimetry systems face, is that portal dosimetry is underutilized in radiotherapy clinics. In 2017, a European Society for Radiotherapy and Oncology (ESTRO) Task Group for *in vivo* dosimetry was established, with the aim of identifying the main reasons for the clinical underutilization of *in vivo* dosimetry methods (with a focus on EPID-based portal dosimetry) and to define requirements for *in vivo* dosimetry systems necessary for increased clinical adoption. This shows that there is a general interest in the radiotherapy community for advancing the field of EPID-based portal dosimetry, but that there are still some hurdles that need

to be taken. These hurdles are related to various aspects of portal dosimetry, such as automation of all parts of the workflow, understanding and reduction of uncertainties, interpretation of results and improvement of error detection. The methods presented in this thesis overcome some of these hurdles, especially those related to uncertainties and interpretation of results for improved error detection.

One of the reasons for the underutilization of portal dosimetry is that the uncertainties, sensitivity and specificity of these methods are often unknown. Moreover, interpretation of the results remains difficult as multi-dimensional information obtained with portal dosimetry is usually reduced to a few metrics to remain manageable for human interpreters. The research in this thesis fills these gaps and proposes novel methods for solving these issues, making portal dosimetry an even more attractive method for treatment verification and potentially increasing its clinical utilization.

To increase the clinical employment of portal dosimetry systems, their error detection capabilities need to be systematically investigated, quantified and reported. On the one hand, this implies analyzing the uncertainties, sensitivity and specificity of implemented portal dosimetry methods, as was done in the first part of this thesis. Only if vendors of portal dosimetry software invest in uncovering these aspects for their portal dosimetry solution in similar manners, and clearly report their findings, can utilization of portal dosimetry be improved. The capabilities and limitations of portal dosimetry systems need to be clear to the clinical users, and the methods presented in part I of this thesis can be used as a framework for quantifying these.

On the other hand, sophisticated methods for interpretation of portal dosimetry results are needed. Vast amounts of data are produced when portal dosimetry is used in a radiotherapy clinic, necessitating automated methods for analyzing these results and detecting relevant deviating cases. Currently, analyzing portal dosimetry results is often a task of medical physicists, who have to manually assess flagged cases. However, as simple threshold methods based on reduced information are used for flagging, there are many false positive cases, and an unknown number of false negatives. With the more sophisticated methods developed in part II of this thesis, the number of false positive and false negative cases will be reduced, improving clinical workload and minimizing the risk of missing relevant deviations.

The application of artificial intelligence (AI) for classification of errors in portal dosimetry is a novel topic, where many aspects still have to be explored. However, part II of this thesis shows that it is a promising road to follow. Advanced methods for error detection as described in this thesis should be added to existing portal dosimetry software packages, although more external validation is needed first, to ensure generalizability and transferability of these methods to different radiotherapy institutes. Underlying differences in clinical practice can make it difficult to provide one model that will be relevant for many different radiotherapy institutes. Although this may be an issue, it also provides an opportunity for standardizing criteria for error detection among centers and removing subjectivity from this process.

An ideal portal dosimetry solution should include AI models for error classification, of which the error detection capabilities have been quantified, such that it is immediately clear to the clinical user what the uncertainties of the methods are, and which errors can be detected and which cannot. Such plug-and-play solutions

will increase the interest of the radiotherapy community in portal dosimetry, as they will provide a straightforward way of verifying and improving complex radiotherapy treatments, saving time and workload compared to current portal dosimetry solutions. This thesis is among the first to study the application of AI models for error detection in portal dosimetry, and a vast amount of work remains to be done. Further development of these models towards an ideal portal dosimetry solution also requires effort from vendors, as well as clinical users and international societies such as ESTRO.

The research in this thesis has been performed within multiple fruitful research agreements with Varian Medical Systems (Palo Alto, CA, USA); one of the largest manufacturers of medical radiotherapy devices and software. In previous research agreements, portal dosimetry methods were developed and several of these models have been acquired by Varian. This acquisition and the continued research collaboration demonstrates the interest of a large player in the radiation oncology field in these treatment verification methods, which will lead to the development of a commercial product for portal dosimetry based on the research performed at Maastro. This thesis is part of this ongoing collaboration, and evaluates aspects of portal dosimetry that are needed for making a successful commercial product. These aspects are quantification of the error detection capabilities of the portal dosimetry methods and development of novel classification methods for improved error detection. Even though the results of this thesis are specific for Varian linacs and EPIDs, the methods can be extended and applied to linacs and EPIDs of other vendors.

Although radiotherapy is already a safe treatment option, detection of errors, even if they are small, enhances treatment quality and provides potential for adaptive radiotherapy, hence increased personalization of treatment. Ultimately, an advanced portal dosimetry solution should and will benefit patients, as errors in their radiotherapy treatment can reliably be detected and corrected, preventing underdosing the tumor and/or overdosing healthy tissues. This is in line with one of the goals of Maastro (Maastricht, The Netherlands), where this research was performed, which is "to reduce the chance of side effects and recurrence of the tumor, through the use of, among others, dose-guided adaptive radiotherapy".