PhD Thesis Title: A Generalized, Modular Approach to Treating Moving Tumors with Ion Beams

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ABSTRACT:

Introduction: Despite advancements in cancer therapy, certain indications continue to have a poor prognosis, including cancers of the thorax. Existing methods for treating moving tumors with carbon ions have shown promise but require technologically complex facilities and still have inherent limitations to mitigating tumor motion. The goal of this dissertation was to develop and test a safe, portable, and modular motion-synchronized dose delivery system (M-DDS) and its peripheral components as a framework for studying motion mitigation with ion beams.

Methods: We designed and integrated a motion-synchronized radiotherapy approach, called multi-phase 4D delivery (MP4D), as modular units of a clinical dose delivery system. The MP4D approach was integrated into a research facility and the facility was redesigned for developing and testing new cancer therapy technologies. We performed a comprehensive risk assessment for the M-DDS and validated the performance of the MP4D approach experimentally. Finally, we compared MP4D to other delivery strategies in terms of dosimetric quality and projected therapeutic outcomes.

The prototype system was implemented and characterized at GSI Helmholtzzentrum für Schwerionenforschung (GSI) and National Center for Oncological Hadrontherapy (CNAO). The functionality and performance were confirmed through a series of tests. Validations revealed that MP4D produces quantitatively superior dosimetric quality and projected therapeutic outcomes. Additionally, we determined that the MP4D dose delivery strategy compensated for heterogeneous anatomical motion with minimal dose distribution degradations. Our safety analysis revealed several risks that are unique to MP4D; appropriate solutions were implemented and tested.

Results: The major findings of this study are that the MP4D approach delivered conformal, motion-synchronized beams with acceptable performance, dosimetric quality, safety and projected therapeutic outcomes. We demonstrated that MP4D may become a suitable strategy for conformal, motion mitigation in clinical radiotherapy.

Conclusions: The modular design of the M-DDS allows for integration into a variety of facilities, and the MP4D methods presented can be utilized at any ion therapy center that operates with a similar delivery system. The generalized and modular design of the M-DDS provides a framework for testing a variety of motion mitigation and other therapy approaches. This work, taken together, provides a comprehensive pre-clinical study on the modular, motion-synchronized dose delivery system for delivering conformal dose distributions to moving targets.

References to author publications that relate specifically to the dissertation:

1. **Lis M**, Newhauser W, Donetti M, Wolf M, Steinsberger T, Paz A, and Graeff C. (2021) Dosimetric Validation of a System to Treat Moving Tumors Using Scanned Ion Beams That Are Synchronized with Anatomical Motion. Front. Oncol., 08 September 2021, Sec. Radiation Oncology, Volume 11 – 2021. doi: 10.3389/fonc.2021.712126
2. **Lis M**, Newhauser W, Donetti M, Wolf M, Steinsberger T, Paz A, and Graeff C. (2021) Preliminary tests of dosimetric quality and projected therapeutic outcomes of multi-phase 4D radiotherapy with proton and carbon ion beams. Physics in Medicine & Biology, Volume 66 (23). doi:10.1088/1361-6560/ac36e7
3. **Lis M**, Newhauser W, Donetti M, Durante M, Weber U, Zipfel B, Hartmann-Sauter C, Wolf M, and Graeff C. (2021) A facility for the research, development, and translation of advanced technologies for ion-beam therapies. Journal of Instrumentation, Volume 16(03): T03004. doi 10.1088/1748-0221/16/03/T03004
4. **Lis M**, Newhauser W, Donetti M, Wolf M, Steinsberger T, Paz A, Durante M, and Graeff C. (2021) A Modular System for Treating Moving Anatomical Targets with Scanned Ion Beams at Multiple Facilities: Pre-Clinical Testing for Quality and Safety of Beam Delivery. Front. Oncol., 19 March 2021, Sec. Radiation Oncology, Volume 11 – 2021. doi: 10.3389/fonc.2021.620388
5. **Lis M**, Donetti M, Newhauser W, Durante M, Dey J, Weber U, Wolf M, Steinsberger T, and Graeff C. (2020) A modular dose delivery system for treating moving targets with scanned ion beams: Performance and safety characteristics, and preliminary tests. Physica Medica, Volume 76:307-16. doi: 10.1016/j.ejmp.2020.07.029