2023 Physics Workshop: Science in Development

Temporal optimization and personalization of the radiation treatment course

13-14 October 2023, Turin, Italy

Chairs: *Thomas Bortfeld, Jan Unkelbach*

For many decades, the design of radiotherapy (RT) treatment plans has revolved around spatial optimization of the dose to maximize tumor coverage while sparing nearby healthy tissues. By contrast, the question of how to optimally deliver dose over time has been studied much less. Since the initial days of RT, most patients with a certain type of cancer have received the same amount of radiation dose distributed equally over a predetermined number of fractions. Even though more patients get treated with hypo-fractionation, thanks to modern treatment techniques to spare normal, the paradigm of uniform fractionation remains unchanged. The Temporal Optimization of Radiotherapy (TEMPO) workshop discussed ideas and approaches to design and optimize radiotherapy schedules that deviate from this traditional paradigm.

Our workshop brought together 20 participants from medical physics, radiation oncology, and mathematics disciplines. Our engagement started with an online (pre)meeting session on September 26, during which the main topics of the workshop were introduced by the workshop's organizers, Thomas Bortfeld (Massachusetts General Hospital, USA) and Jan Unkelbach (University of Zurich, Switzerland):

- **Optimal Stopping**: how to dynamically monitor and biologically adapt to patients' response during RT using continuous biomarker information flow.
- **Beyond uniform fractionation**: what rationales are there to deliver different doses or distinct dose distribution in each fraction to optimally exploit fractionation effects in tumor and normal tissues .
- **Managing cancer as a chronic disease**: how to optimize the treatment monitoring and delivery of radiation over a longer course of treatment in oligometastatic patients.

The participants were then assigned to one of the topics to form focus groups and were asked to provide a short "pitch talk" for the workshop.

During the 2-day workshop in Turin, the discussion on each topic was kicked off by a keynote presentation, followed by 5-minute pitch talks by the participants. The first session (Optimal Stopping, Day 1) started with a presentation by Iuliana Toma-Dasu (Stockholm University).

***Figure 1**. Keynote presentations by I. Toma-Dasu (left) on Optimal Stopping and N. Torelli (right) on Spatiotemporal Optimization. Photo credit: T. Bortfeld.*

She discussed the concept of biologically adapted RT treatment planning using dynamic (PET) image acquisitions and introduced the concept of effective radiosensitivity (α_{eff}) for in-treatment assessment of tumor response. On the second topic (Beyond uniform fractionation, Day 1-2), Nathan Torelli (University of Zurich) discussed the rationales to deviate from the paradigm of equal fraction doses and dose distributions. Finally, in the third topic (Cancer as a chronic disease, Day 2), Maximillian Niayzi (Tübingen University Hospital) shared his thoughts on and his vision for the future direction of RT in managing metastatic cancer, as well as an overview of the emerging (non-conventional) approaches to RT delivery. The pitch talks further extended the discussion on each topic and tackled the challenges and opportunities from multiple complementary angles (see Figure 2 for an overview of the subjects covered).

After that, the discussion was opened to the broader group. As the talks progressed, three distinct threads emerged as the key drivers of the discussion:

- **Data availability**: Some prognostic and predictive biomarkers already exist with potential to guide treatment personalization during RT. They include, among others, Δ-imaging signatures from (e.g., PET tracer uptake, tumor shrinkage index, change in the diffusion weighted MRI signatures) and Δ-blood-borne cytokines and proteomics (e.g., ctDNA, cardiac-specific troponin). The crux of the problem is to translate these dynamic signals into a reliable surrogate for RT response. Mechanistic and machine learning modeling could offer some potential solutions.

- **Temporal adaptation**: how to "act" on the biomarker information, i.e., adapt the treatment course to patients' response? Besides accounting for biomarker and modeling uncertainties, an important consideration is navigating the tradeoff between effective treatment adaptation while staying within

some “reasonable neighborhood” of current clinical practice. Deviating from conventional planning “in small, measured steps” could offer a logical starting point.

- **Clinical validation**: how to design effective clinical trials to test these concepts while minimizing the data burden on single institutions? One potential solution could be to design parallel (distributed) “small-scale” trials across many institutions to distribute (and reduce) the data burden and minimize the overall cost of running the trial.

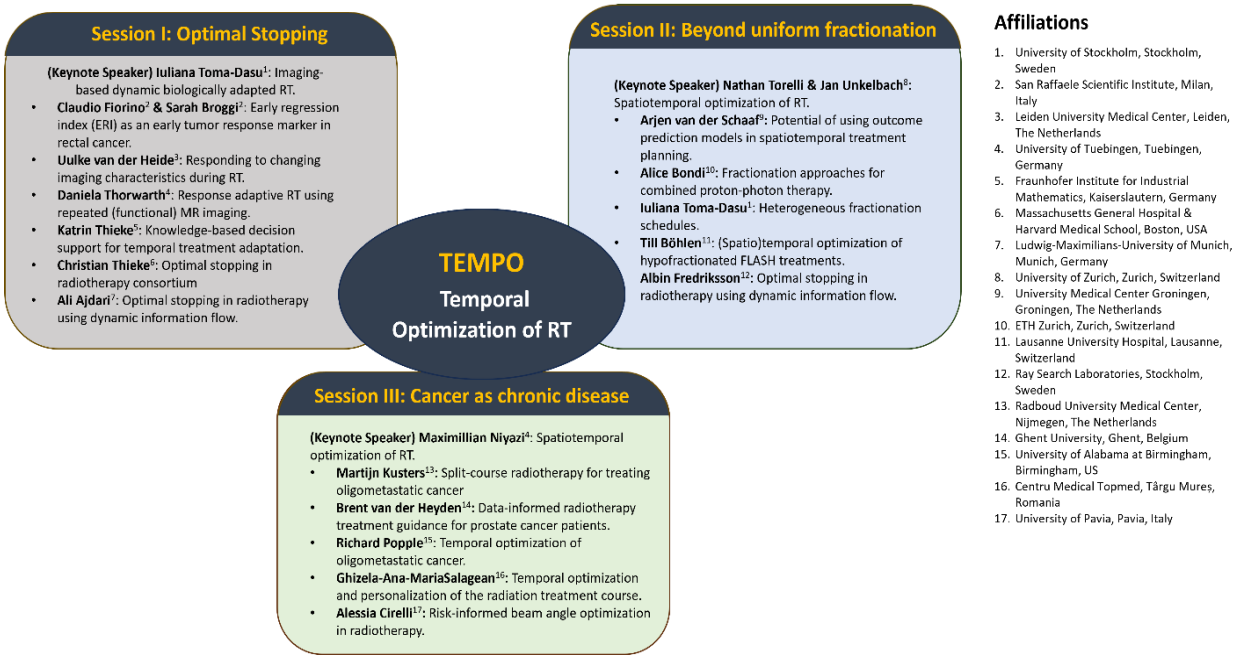

***Figure 2**. Presentations and "pitch talks" by the participants.*

At the end of the workshop, the consensus was that to bring temporal optimization into clinic, more work needs to be done in each of these three fronts: Biomarker data, Treatment Adaptation, and Clinical Trial Design. The next steps included establishing complementary workgroups for leading the effort on each front, creating a repository of potential biomarkers across the ESTRO (and potentially AAPM) institutions, and writing a white paper based on the workshop’s conclusions. As the result of the workshop, two concrete projects are currently underway between Tübingen-Milan-Boston (clinical trial design) and Kaiserslautern-Boston (treatment adaptation).

***Figure 3**. Group discussion. Top: Day 1-Listening to U. van der Heide on biomarker-based mid-RT adaptation (photo credit: T. Bortfeld); Bottom: Day 2-T. Bortfeld and M. Niayzi discussing the future steps of TEMPO (photo credit: C. Thieke).*

Ali Ajdari, Ph.D.
Instructor
Department of Radiation Oncology
Harvard Medical School
Massachusetts General Hospital