

## Short project description

Current state of the art risk modelling of side effects from radiation therapy predominantly involves institutional series using a low-grade endpoint of toxicity on a limited time scale, often only months. The challenge is that more severe events are too rare for modeling purposes and institutional series with detailed dosimetry, long term follow-up and reliable toxicity scoring are extremely rare. The problem is twofold: First, the severity of acute complications used in modeling are often not the main clinical concern. Second, milder complications are certainly a concern if they persist, but chronic complications may appear long after patients have completed follow-up in institutional series. Important registry studies try to address this problem(1-4), but have the limitation of very rudimentary information about treatment exposure and are therefore limited in informing the optimal choice of radiation dose prescription.

We propose a move beyond current state of the art as follows: Modern informatics systems allow automated extraction of dose data and the Danish registries allow cross-linkage of such dosimetric data with prescription medicine, hospital admission records or mortality data. See Figure 1 for pilot data. We propose deep learning-based segmentation methods developed under this grant as the necessary bridge to gain detailed knowledge of organ exposure to correlate with the adverse effects as observed through registry data. In turn, such knowledge is required for clinical utility through the avoidance of critical substructures in future radiotherapy planning and the comprehensive balancing of exposure to multiple adjacent organs at risk and target coverage(5-7). Clearly, it is also necessary to increase our understanding of exactly when the dose sparing of the normal tissue surrounding the target becomes too much and starts causing a decrease in the efficacy of radiotherapy in terms of oncologic outcome.

1. S. C. Darby *et al.*, Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* **368**, 987-998 (2013).
2. A. K. Ng, L. B. Kenney, E. S. Gilbert, L. B. Travis, Secondary malignancies across the age spectrum. *Semin.Radiat.Oncol.* **20**, 67-78 (2010).
3. R. C. Reulen *et al.*, Long-term cause-specific mortality among survivors of childhood cancer. *JAMA* **304**, 172-179 (2010).
4. L. B. Travis, W. Demark Wahnefried, J. M. Allan, M. E. Wood, A. K. Ng, Aetiology, genetics and prevention of secondary neoplasms in adult cancer survivors. *Nat Rev Clin Oncol* **10**, 289-301 (2013).
5. N. P. Brodin *et al.*, Life years lost-comparing potentially fatal late complications after radiotherapy for pediatric medulloblastoma on a common scale. *Cancer*, (2012).
6. L. B. Stick *et al.*, Joint Estimation of Cardiac Toxicity and Recurrence Risks After Comprehensive Nodal Photon Versus Proton Therapy for Breast Cancer. *Int J Radiat Oncol Biol Phys* **97**, 754-761 (2017).
7. A. Modiri *et al.*, Individualized estimates of overall survival in radiation therapy plan optimization - A concept study. *Med Phys*, (2018).