Causal inference models for the prediction of radio-induced toxicity after breast cancer radiotherapy

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Background

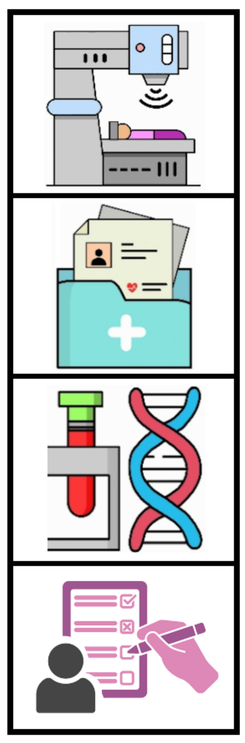
Breast cancer (BC) is the most diagnosed cancer in Europe and the leading cause of cancer death in women.
Randomised trials established the role of radiotherapy (RT) following breast-conserving surgery and adjuvant RT as a standard of care. RT planning and advanced delivery techniques allow targeting the breast while minimising the doses to organs at risk.
Yet, **some doses unavoidably reach normal tissues, putting BC patients at risk of radio-induced toxicity**.

State of the art

The risk of developing toxicity is highly variable among individuals, reflecting its multifactorial origin. Key determinants include the cumulative dose delivered to healthy tissues, the individual's genetic background, pre-existing clinical conditions, and the concomitant use of systemic oncological therapies.
Causal inference enables the integration of patient-specific clinical, imaging, genetic, and transcriptomic **data**, enhancing the ability **to identify the causal effect of radiation doses and other patient-specific features on the normal tissue functional damage.**

Preliminary data

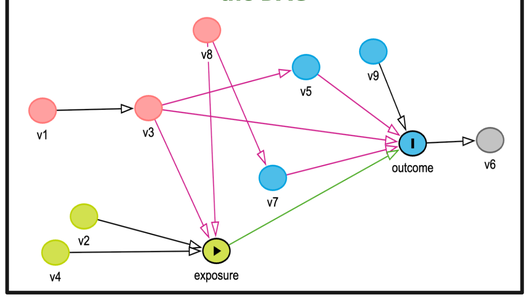
- **2034 breast cancer patients**



- **Dosimetric features** from treatment plans and CT scans
- **Clinical data** including patients' lifestyle, comorbidities and breast characteristics
- **Genomic data** from SNPs associated with late RT-induced toxicity
- **Toxicity information** till 7-year follow-up

Design of the study and first results

Describe the causal-effect relations through the DAG

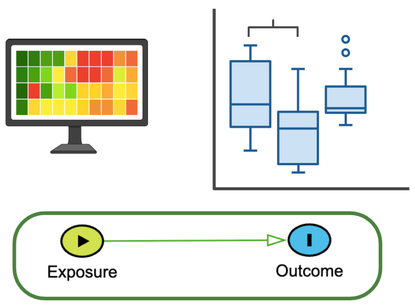


Identify the variables that could be excluded in order to accurately assess the true effect of the exposure on the outcome.

Minimal sufficient adjustment sets for estimating the total effect of exposure on outcome:

- v3, v7
- v3, v8

Perform statistical analysis on the remaining variables to estimate the true causal effect and address the causal question defined a priori



1. After building a structured dosimetric and multi-omic database, we will develop multiple **Directed Acyclic Graphs (DAGs) to represent current knowledge of biological and behavioural systems** related to the specific adverse events under investigation.
2. **These DAGs will help identify variables with a confounding effect, as well as those directly influencing the risk of toxicity**, thereby guiding the definition of inclusion criteria for the primary analysis (and for any potential sub-analyses).
3. Based on statistical analyses of the predictor variables identified through the DAGs, we will design a **Target Trial Emulation** by formulating a clear causal question and outlining the protocol for a hypothetical randomised trial to address it.

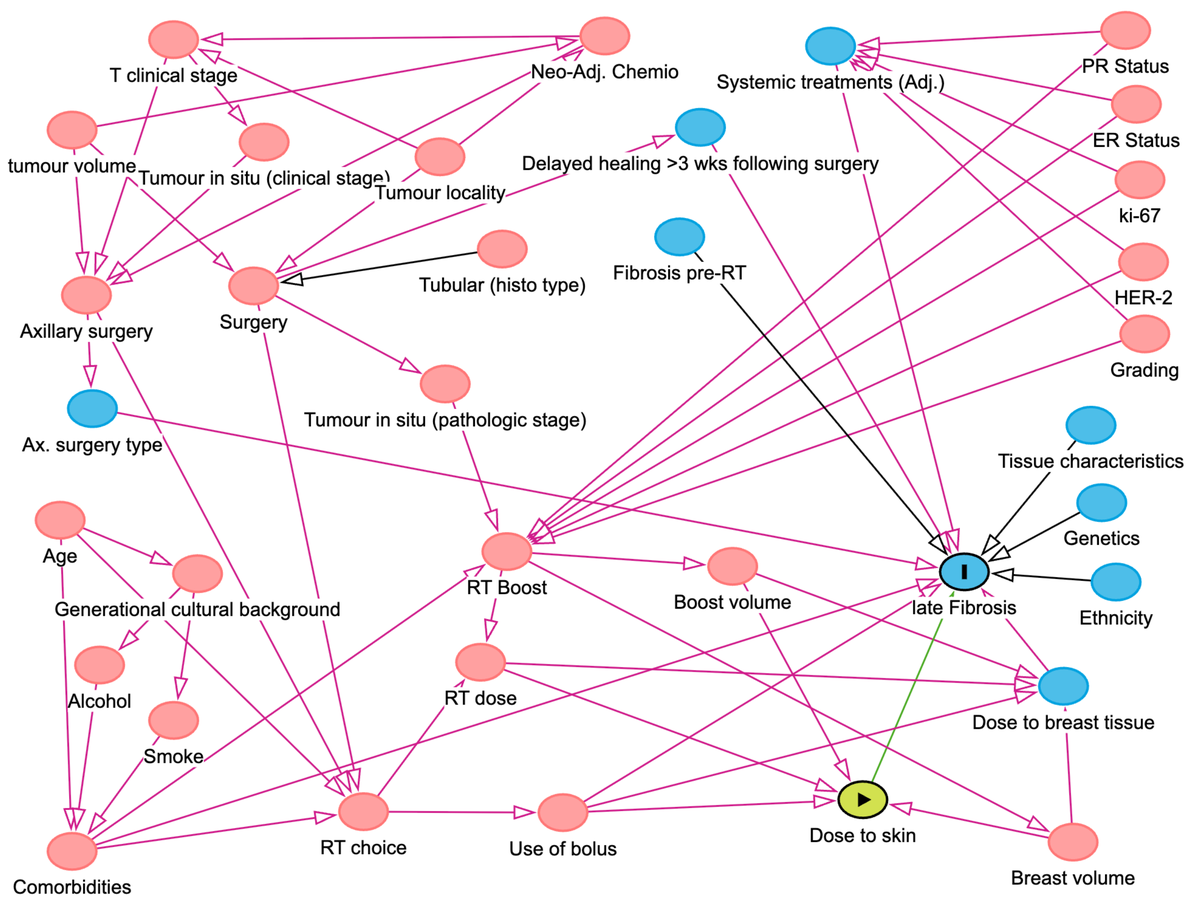


Figure 1. First DAG developed for late fibrosis. Developed through cross-disciplinary sessions, this DAG aims to identify the appropriate adjustment sets for estimating the total and direct effects of the dose to the skin (exposure) on late fibrosis (outcome).

Acknowledgements

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