Application of causal inference techniques for accurate estimation of the causal effect of dose to the heart base on overall-survival in lung cancer

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Introduction

- Voxel-based analysis (VBA) aims to analyse how spatial dose distributions in a given patient cohort associate with treatment outcomes.
- VBA has in the past 10 years been utilized to study spatial radiotherapy (RT) dose-toxicity effects in cancer research.
- Multivariable models used in this approach are not geared to infer causality.

Aim

Produce a directed acyclic graph (DAG) to assess whether the original model using in McWilliam et al., 2017 [1] can be interpreted causally, and devise a minimal adjustment set to address bias on the effect.

Re-analyse the data from 1100 patients treated with 55Gy in 20 fractions between 2010 and 2013 [1] with the aim of causally interpreting the effect of dose to the heart base on overall-survival.

Directed acyclic graphs (DAGs)

- DAGs visualise causal effects.
- Causal effects are directional and represented with arcs →
- Experts and clinicians were consulted to account for undocumented clinical decisions and reach consensus on causal effects.
- All variables relevant to the effect of heart base dose on survival were included on the DAG, whether measured in the paper or not.
- The McWilliam 2017 adjustment set comprised of **sex, age, baseline performance status, gross tumour volume (GTV), T stage, N stage, induction chemotherapy and lung dose.**
- Biasing pathways on the DAG remained open when adjusted with covariates from the McWilliam paper.
- Figure 1 shows the minimal adjustment set - the fewest covariate adjustments required to close biasing pathways but keep causal pathways open (**green**).
- Minimal adjustment set: **T stage, GTV, tumour location, and RT modality.**
- **Prescribed dose** is controlled for by the study design and thus is present in both adjustment sets.
- **Lung dose** is a suspected mediator, adjusting for it impedes measurement of the total effect.

The total causal effect of delivered radiotherapy dose to the heart base region on overall survival (OS)

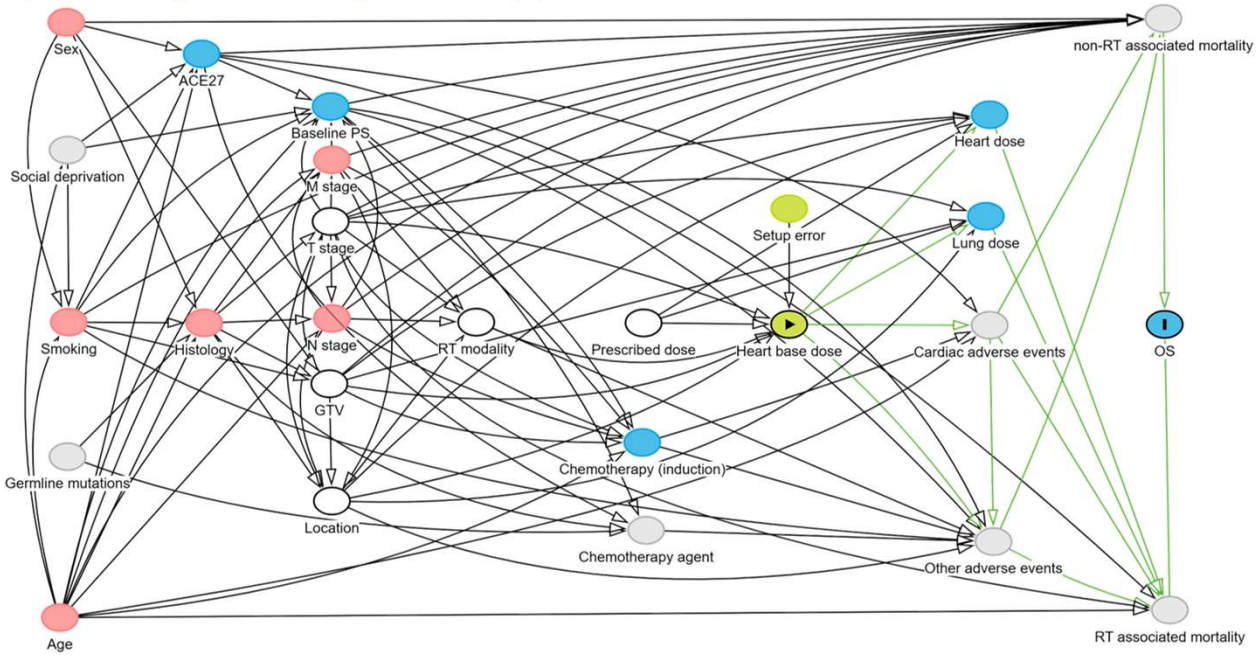

Figure 1: *DAG showing effects on the target estimand: the total causal effect of delivered radiotherapy dose to the heart base region on overall survival (OS) in a sample of 1100 patients receiving RT for lung cancer. The DAG has been minimally adjusted to close all biasing pathways without closing causal pathways (**green**). Confounders are shown with **red** nodes, minimal adjustment set shown with **white** nodes.*

Cox regression modelling

- Multiple imputation was utilised to address missing data.
- Cox regression analysis was carried out using the McWilliam 2017 model adjustments and the model pertaining to a minimal adjustment set.
- Dose to region in the base of the heart **violated the proportional hazards assumption.**
- Schoenfeld residuals plots showed the direction of the effect of dose to the heart base on survival changed from +ve to –ve at ~18 months.
- Separate hazard ratios for these two phases were calculated using a **time split at 18 months**; proportional hazards held.
- Sensitivity testing with 12- and 24-month splits produced models which violated proportional hazards.
- Table 1 shows that **≤18 months follow up, excess dose to the heart base region increases risk of mortality.**
- The minimal adjustment set produced a **lower estimate and narrower CIs** with a **ratio of 1.005** when compared with the McWilliam 2017 adjustments in the first phase (≤18 months).

McWilliam 2017 regression				Minimal adjustment regression			
≤18 months		>18 months		≤18 months		>18 months	
HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
1.139 (1.054-1.230)	0.001	0.952 (0.868-1.045)	0.304	1.133 (1.065-1.207)	<0.001 ***	0.948 (0.873-1.030)	0.207

Table 1: *Hazard ratios (HR) and p values pertaining to dose to the heart base region from multivariable cox regression analysis using the two models specified, split at 18 months follow up.*

Conclusions

- This work exemplifies how DAGs can be used to assess bias and build models in VBA research which can infer causality.
- The multivariable model utilised in McWilliam 2017 is not causally interpretable due to biasing pathways remaining open and causal pathways closed.
- The effect of excess dose to the heart base was shown to be time dependent, increasing risk of mortality up to 18 months follow up. To our knowledge, this result has not been reported elsewhere in the literature.
- Occurrence of severe RT associated cardiotoxicity at a median follow up of 7-11 months [2] [3] has been observed in the literature, and acute cardiotoxicity has been associated with poorer OS [4].

Future Work

- Repeat methods in another sample of lung cancer patient to see whether the time dependent effect is replicable
- Investigate a possible clinical rational behind this time dependence

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