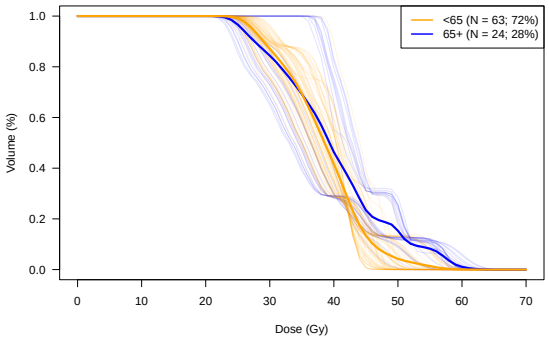
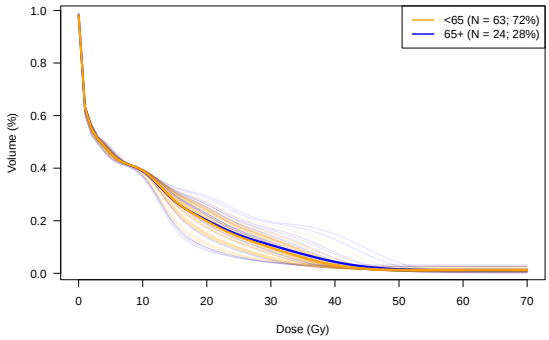
Illustration on a simulated cohort of anal and perianal cancer patients

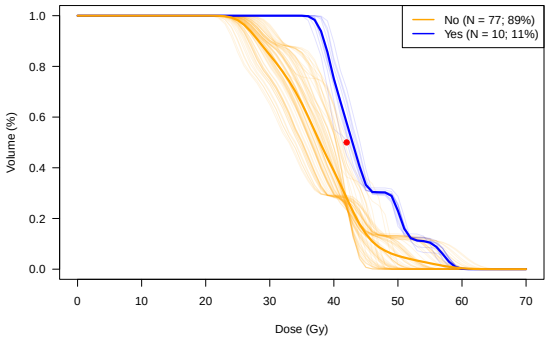
As the dataset used to illustrate the methods in "a marginal model for normal tissue complication modeling" by Tang, Liu, Hosni, Kim, and Saarela cannot be made publicly available, a simulated dataset based on a cohort of patients with anal and perianal cancer treated at the Princess Margaret Cancer Centre between 2008-2013 is available for reproducibility of the methods on `https://github.com/thaisontang/marginalntcp`. Acute gastrointestinal and genitourinary toxicities and dose distribution of OARs (skin & bladder) were available for 87 patients.



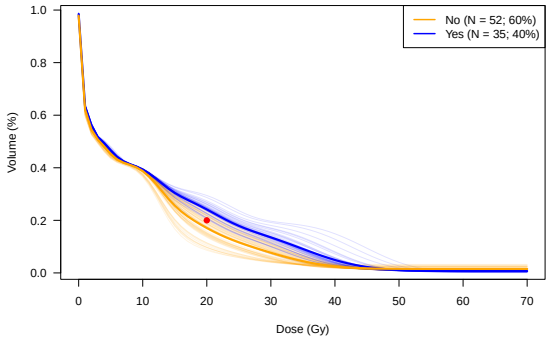
(a) Bladder DVHs stratified by age at diagnosis at 65 years



(b) Skin DVHs stratified by age at diagnosis at 65 years



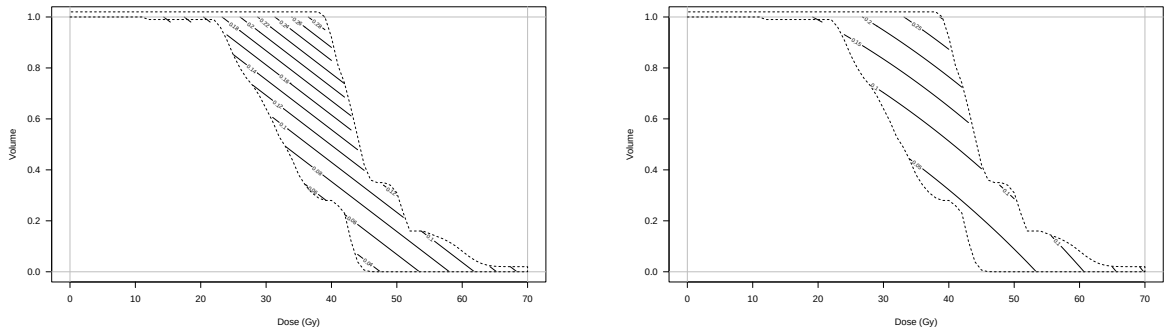
(c) Bladder DVHs stratified by ≥Grade 2 acute genitourinary toxicity



(d) Skin DVHs stratified by ≥Grade 3 acute skin (perinanal, inguinal, or genital) toxicity

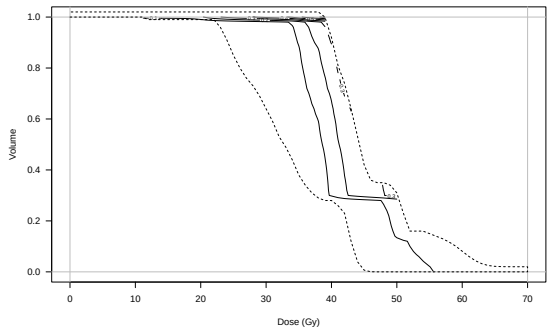
Figure 1: Dose-volume histograms (presented as complementary CDFs) of 87 anal canal cancer patients. Pointwise average DVHs are illustrated by darker, solid lines. The red dot illustrates the coordinate employing the stochastic intervention.

10 patients had Grade ≥2 acute genitourinary toxicity, with these patients, on average, having higher bladder radiation dose than those without toxicity (Figure 1c). 35 patients with Grade ≥3 acute skin (defined as perianal, inguinal, or genital) toxicity also had, on average, higher skin radiation dose (Figure 1d). 24 patients had their cancer diagnosis over the age of 65 and exhibited higher radiation dose for both the skin and the bladder than those diagnosed under 65. There was greater variation in bladder dose distributions in comparison to skin dose distributions.

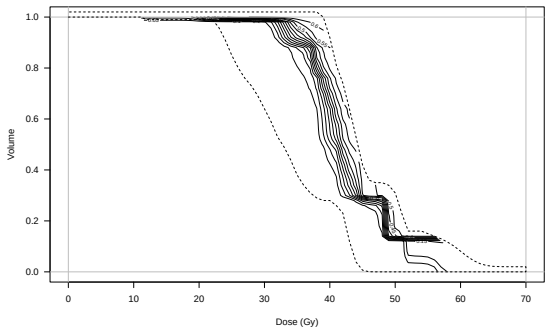


(a) Logistic

(b) Polynomial logistic



(c) Additive

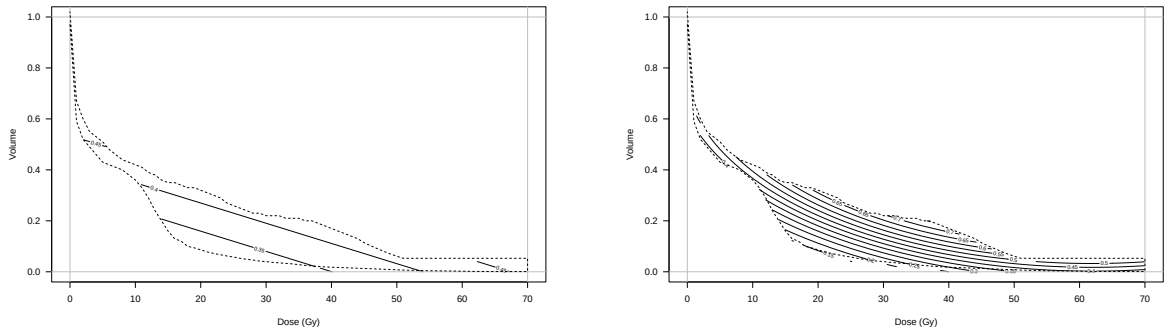


(d) Bivariable monotone

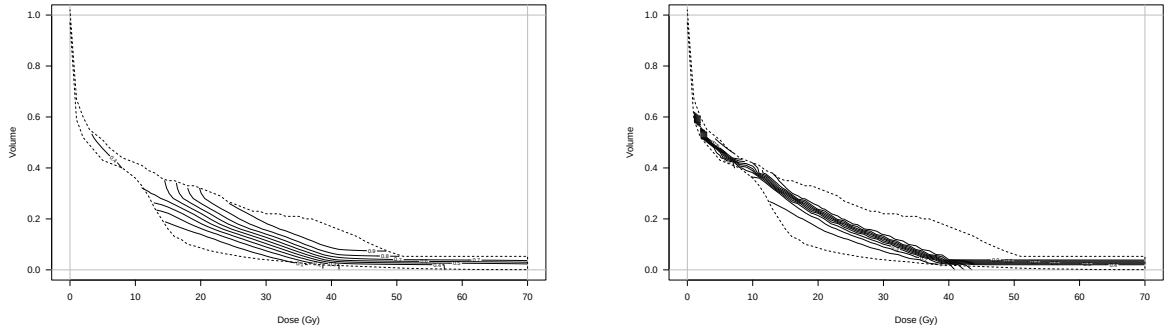
Figure 2: Contour plots for the model-estimated pointwise causal NTCP for genitourinary toxicity at each dose-volume coordinate within the bladder DVH domains (outlined by dotted lines) in anal canal cancer patients.

We fit MSMs to estimate the pointwise causal NTCPs for genitourinary and skin toxicity and illustrated these estimates using contour plots. We also considered hypothetical stochastic interventions on the treatment plans where volume of the bladder exposed to greater than 42 Gy was restricted to less than or equal to 50% ($G_{42\text{ Gy}} \leq 0.5$) and the observed volume of the skin exposed to greater than 20 Gy restricted to less than or equal to 20% ($G_{20\text{ Gy}} \leq 0.2$). MSMs with linear, polynomial, additive and bivariable monotone specifications for dose and volume effects were fitted using the `monoreg` package. We considered age (under/over 65 years) as a potential confounder. Bootstrap with 1000 resamples was used to generate confidence intervals.

The contour plots of model-based estimates of bladder and skin pointwise-causal NTCP are shown in Figures 2 and 3, respectively. The NTCP estimates for the bladder exhibit bivariable monotone increasing surfaces under additive and bivariable monotone model specifications, suggesting that treatment plans reducing dose or volume pointwise yield a reduction in the NTCP (Figure 2). The contours between the parametric specifications, additive and bivariable monotone models are visually quite different, suggesting that the true underlying surfaces may be better captured with increasing model flexibility. The bivariable monotone functional form resulted in the best model fit (lowest Brier score and DIC) (Table 1).



(a) Logistic **(b)** Polynomial logistic



(c) Additive **(d)** Bivariable monotone

Figure 3: Contour plots for the model-estimated pointwise causal NTCP for gastronintestinal toxicity at each dose-volume coordinate within the skin DVH domains (outlined by dotted lines) in anal canal cancer patients.

Table 1: Estimates of the risk ratio for the stochastic causal NTCP under the truncated (bladder volume ≤ 0.5 at 42 Gy; skin volume ≤ 0.2 at 20 Gy) and observed interventions of the DVH and associated in-sample performance metrics.

DVH	Model	Causal Risk Ratio	In-Sample Metric			
		Estimate (95% CI)	Brier	Deviance	k	DIC
Bladder	Logistic	0.84 (0.59, 1.15)	6.65	2630.57	4.47	2635.04
	Polynomial	0.57 (0.39, 0.80)	6.59	2598.45	8.21	2606.66
	Additive	0.50 (0.23, 0.87)	4.87	2015.56	53.73	2069.29
	Bivariable	0.05 (0.03, 0.10)	4.09	1632.54	129.96	1762.50
Skin	Logistic	0.85 (0.79, 0.90)	23.17	8100.33	3.89	8104.22
	Polynomial	0.70 (0.61, 0.80)	21.52	7652.47	1796.10	9448.57
	Additive	0.45 (0.36, 0.54)	18.96	6903.95	96.43	7000.38
	Bivariable	0.25 (0.10, 0.45)	15.15	5766.81	1129.50	6896.31

k = effective number of MCMC parameters, DIC = Deviance Information Criterion

For the skin, all four model specifications produced bivariable monotone increasing NTCP estimates (Figure 3). However, the model fit statistics still indicated some differences between the models, with bivariable monotone model resulting in the best fit in terms of Brier score and DIC (Table 1). From contour plots produced by the bivariable monotone model, the NTCP had the dose distribution of all patients been intervened such that exactly 20% of the bladder received at least 50 Gy of radiation is approximately 50% (Figure 2d), while the NTCP had the dose distribution of all patients been intervened such that exactly 20% of the skin received at least 20 Gy of radiation is approximately 10% (Figure 3d). Contours such as the ones presented could guide the placement of dose-volume constraints in lowering marginal NTCP during treatment planning.

The results for the stochastic intervention estimates are also presented in Table 1 as causal risk ratios. Under the bivariable monotone model, the NTCP had the observed skin volume of patients exposed to 20 Gy been restricted to less than or equal to 20% is 0.25 times (95% CI: 0.10–0.45) the NTCP had the skin dose distribution been unrestricted. Overall, the estimated stochastic causal risk ratios across all four models under the skin DVH exhibited a reduction in causal NTCP from the unrestricted dose distribution. The confidence intervals were larger under the additive and bivariable models with the higher variance under the latter. Similarly, the NTCP had the observed bladder volume of patients exposed to greater than 42 Gy been restricted to less than or equal to 50% is 0.05 times (95% CI: 0.03–0.10) the NTCP had the bladder dose distribution been unrestricted.