Supplementary material for Stokkevåg et al., Risk of radiation-induced secondary rectal and bladder cancer following radiotherapy of prostate cancer. Acta Oncol 2015;54:1317–1325.

SC risk models and corresponding model parameters

As a basis for direct relative comparison between the different techniques we applied the OED concept [1, 2] (also referred to as $OED_{rad\text{-}ther}$), i.e. excluding absolute risk factors determining the initial low-dose slope. Our calculations were based on dose-volume-histogram (DVH) export from the treatment planning software. The dose-response relationships included in the subsequent analysis are described in the following with details about the model parameters listed in Table AI:

1. Linear dose-response (LNT):

$$OED_{LNT} = \frac{D_{mean}}{\mathrm{f_{red}}} = \frac{1}{\mathrm{N\ f_{red}}} \sum_{i=1}^{N} D_i$$

where the DVH dose D_i is taken over N calculation points representing the relative organ volume. A linear risk reduction factor was applied at this stage taken from Gonzalez et al. [3].

2. A linear-plateau response [1]:

$$OED_{Lin-Plat} = \frac{1}{\mathrm{N}} \sum_{i=1}^{N} \frac{1 - \mathrm{e}^{-\delta}\ \ D_i}{\delta}$$

with the organ-specific model parameter δ .

3. Organ-specific bell-shaped dose-response for n fractions (competition model) [4]:

$$OED_{Competition} = \frac{1}{\mathrm{N}} \sum_{i=1}^{N} \left(D_i + \frac{{D_i}^2}{\left({}^{\alpha}/_{\beta} \right)} \right) e^{-\left(\alpha_2 D_i + \frac{\beta_2 {D_i}^2}{n} \right)}$$

where the α/β –value and cell survival parameters α_2 and β_2 used were the original model parameters described in Dasu et al. [4].

Age, gender and organ specific risk factors, R, corresponding to the low dose linear increase were subsequently applied in calculating the lifetime attributable risk (LAR):

$$LAR = OED \times R(exposure\ age, gender, organ)$$

The LAR models were developed and intended for low-dose rate (<0.01 mGy/min) and low-dose exposures (<100 mGy) and were originally reduced by a Dose to Dose-Rate Effectiveness Factor (DDREF) of 1.5. For our purpose of estimating risks for in-field organs we excluded this DDREF adjustment. Hence our risk factors were obtained by multiplying the estimated risks reported by Gonzalez et al with a factor of 1.5. The R thereby functioned as the initial slope of our non-linear models, while the slope of the LNT model had a less steep constant increase (according to the reduction of f_{red}). The dose-response relationships are shown in Figure 1.

For the scatter dose adjusted IMPT risk calculations we added stray radiation doses simulated by Fontenot et al [5]. From the latter publication, the equivalent doses for the bladder and rectum were found to be approximately 4.5 mSv/Gy from internally produced neutrons and photons [5], corresponding to about 0.3 Gy(RBE) in our treatment scenario. We therefore adjusted the dose to the volume fractions that by the TPS was reported as lower than this minimum dose level, D_{min}, and used the doses as given by the treatment planning system above this threshold. Subsequently no parts of the bladder or rectum received less than 0.3 Gy(RBE) in the IMPT estimates including scatter doses.

Table AI. Model parameters

	Bladder	Rectum	Unit	Reference
α/β	7.5	5.4	Gy	[4] Table 2
α_2	2.50E-01	2.50E-01	Gy^{-1}	[4] Table 2
β_2	3.30E-02	4.60E-02	Gy^{-2}	[4] Table 2
δ	5.10	0.26*	Gy^{-1}	[1] Table 1
f_{red}	19,78	5,04	-	[3] Table 1
R(50)	1.46E-02	1.65E-03	Gy^{-1}	[6] Table 2b***
R(60)	1.20E-02	1.20E-03	Gy^{-1}	[6] Table 2b***
R(70)	7.35E-03	6.00E-04	Gy^{-1}	[6] Table 2b***
R(80)	2.85E-03	1.50E-04	Gy^{-1}	[6] Table 2b***
D_{min}	0.3**	0.3**	Gy(RBE)	[5] Figure 2

*Colon parameter applied

** estimated from approximately 4.5 mSv/Gy from internally produced neutrons and photons

*** DDREF taken out i.e. table values are multiplied by 1.5

List of references (supplementary material)

1. Schneider U, Kaser-Hotz B. Radiation risk estimates after radiotherapy: application of the organ equivalent dose concept to plateau dose-response relationships. Radiat Environ Biophys. 2005;44:235-9.
2. Schneider U, Kaser-Hotz B. A simple dose-response relationship for modeling secondary cancer incidence after radiotherapy. Z Med Phys. 2005;15:31-7.
3. Berrington de Gonzalez A, Gilbert E, Curtis R, Inskip P, Kleinerman R, Morton L, et al. Second solid cancers after radiation therapy: a systematic review of the epidemiologic studies of the radiation dose-response relationship. Int J Radiat Oncol Biol Phys. 2013;86:224-33.
4. Daşu A, Toma-Daşu I, Franzén L, Widmark A, Nilsson P. Secondary malignancies from prostate cancer radiation treatment: a risk analysis of the influence of target margins and fractionation patterns. Int J Radiat Oncol Biol Phys. 2011;79:738-46.
5. Fontenot J, Taddei P, Zheng Y, Mirkovic D, Jordan T, Newhauser W. Equivalent dose and effective dose from stray radiation during passively scattered proton radiotherapy for prostate cancer. Phys Med Biol. 2008;53:1677-88.
6. Berrington de Gonzalez A, Iulian Apostoaei A, Veiga LH, Rajaraman P, Thomas BA, Owen Hoffman F, et al. RadRAT: a radiation risk assessment tool for lifetime cancer risk projection. J Radiol Prot. 2012;32:205-22.

Results for individual patients

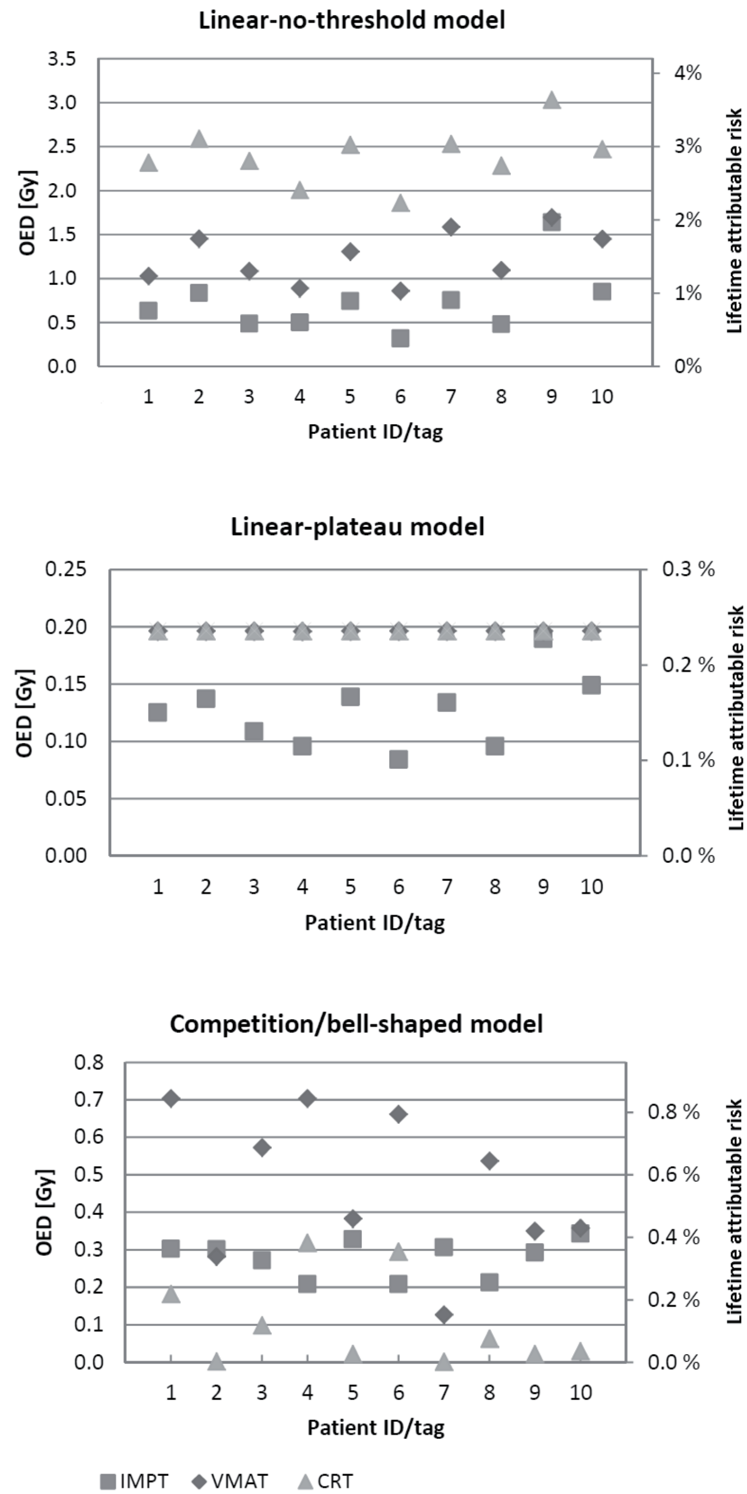

Figure A1. Risk of radiation-induced secondary bladder cancer for individual patients based on exposure at age 60 years.