Secondary cancer risk modelling in photon- and particle-based radiotherapy of cancer

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Application of Secondary cancer risk modelling in photon- and particle-based radiotherapy of cancer

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- Camilla Stokkevåg, PhD, Haukeland University Hospital / University of Bergen, Bergen, Norway

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Radiotherapy and biological modelling

- Aim of RT is to maximise tumour control probability (TCP) while maintaining acceptable normal tissue complication probabilities (NTCPs)

- Use dose-response derived from a patient cohort and apply as predictor in other patients

- For photon therapy dose-responses reasonably well described for many organ systems -> used as reference

- Protons and ions deposit energy differently at the microscopic level compared to photons
  - Enhanced relative biological effectiveness (RBE)

Therapeutic window
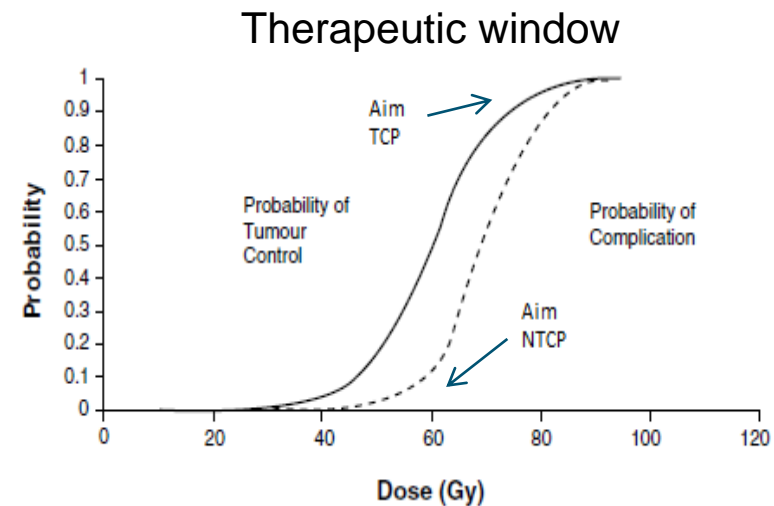
Biological damage on cell nuclei

Tsujii et al. 2014
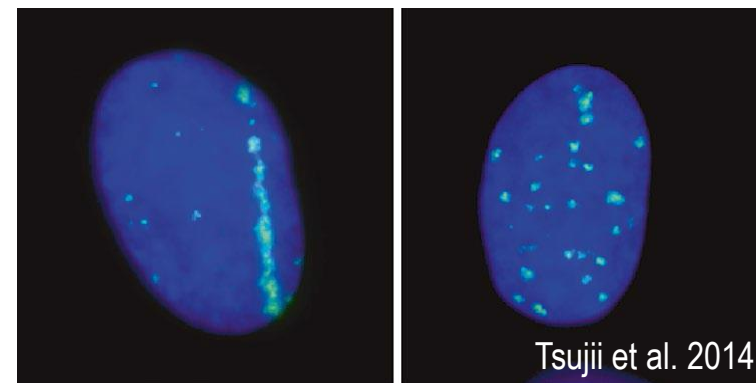
Ions   Photons

Late effects after RT

- RT patients are at risk of experiencing both acute and late morbidities, including effects like radiation-induced secondary cancer that can occur decades after treatment

- More effective cancer treatment has improved survival rates, resulting in more long-term survivors, therefore treatment-induced morbidity more relevant

- RT outcome models increasingly more used to guide future therapy decisions (vs. randomised trials)
  - The 'Dutch model' for NTCP-based patient selection to proton therapy (Langendijk et al)
  - Radiomics / big data

Modelling late effects, incl secondary cancer induction

- The rapid development in radiotherapy calls for predictive modelling of late effects from new techniques

- The dose-response relations used as model input are uncertain

- Extrapolation to RT include several dose-response scenarios

- Radiation-induced cancer risk depends on age at exposure, gender, type of tissue, dose rate and dose homogeneity
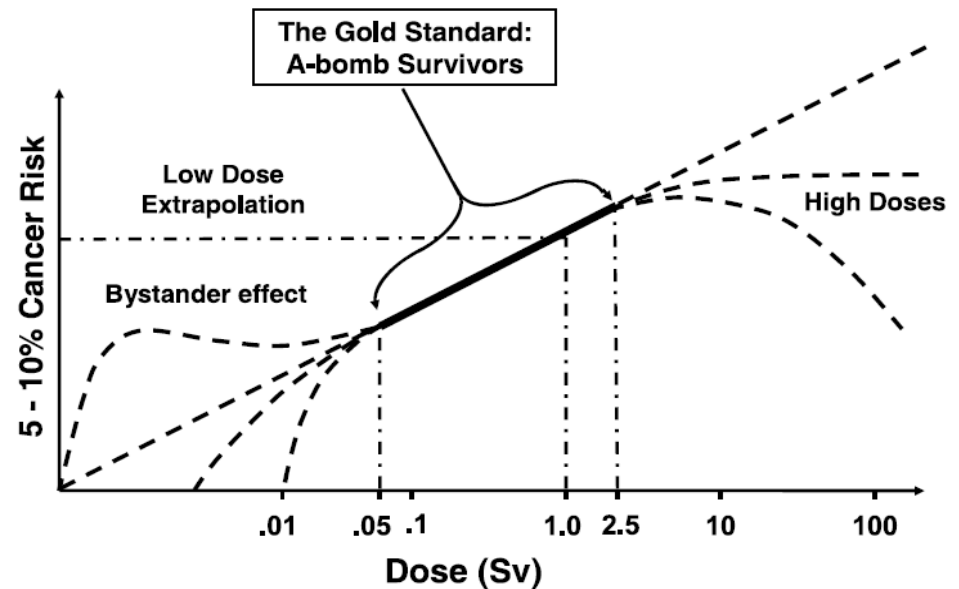
Dose-response relationship for radiation induced carcinogenesis in humans [figure from Hall 2009]

Contents of presentation

- Secondary cancer modelling of **paediatric cranio-spinal irradiation**
  - Comparison of conventional RT with 1st and 2nd generation proton therapy techniques
  - Reasonably well established indication for protons (mostly treated with 1st generation proton therapy)

- Secondary cancer modelling of **localised prostate cancer**
  - Reconstruction of 'old technique', contemporary photons (VMAT), protons and carbon ions
  - Secondary bladder and rectal cancer investigated
  - Influence of organ motion
  - RBE-inclusive model
  - Proton/particle therapy still under investigation

- For both sites, multiple models/parameters were explored

Estimated risk of radiation-induced cancer in paediatric patients following electron, photon and proton therapy

Camilla H Stokkevåg[1,2], Grete May Engeseth[1], Kristian S Ytre-Hauge[2], Dieter Röhrich[2], Odd Harald Odland[1], Ludvig P Muren[3], Marianne Brydøy[1], Liv B Hysing[1], Artur Szostak[2] , Matthew B Palmer[4], Jørgen BB Petersen [3]

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Introduction

- Medulloblastoma is the most common malignant childhood brain tumour and a sub-group of cancer diseases of the central nervous system (CNS)

- Paediatric and young cancer patients are at particular risk of experiencing late effects from treatments due to their long life expectancy and enhanced radiosensitivity
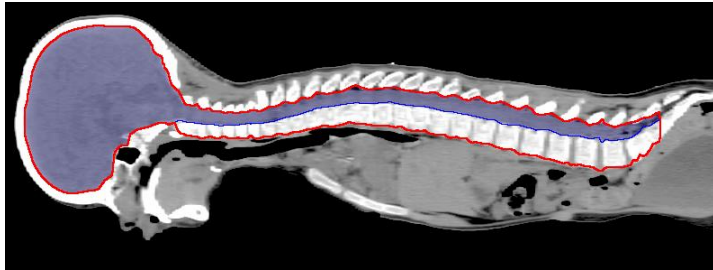

MRI of medulloblastoma

Aims

- Estimate the organ-specific radiation-induced cancer risk after electron, photon and proton radiotherapy for paediatric patients

- Apply multiple models to include a range of possible dose-response scenarios

- Include age- and gender specific estimates

Cranio-Spinal Irradiation (CSI)

Cranio-spinal target volumes. Volume containing cerebrospinal fluid is the primary treatment volume (blue). Expanded age-specific target volume for proton techniques includes the bones of the vertebrae in order to prevent asymmetric growth (red)
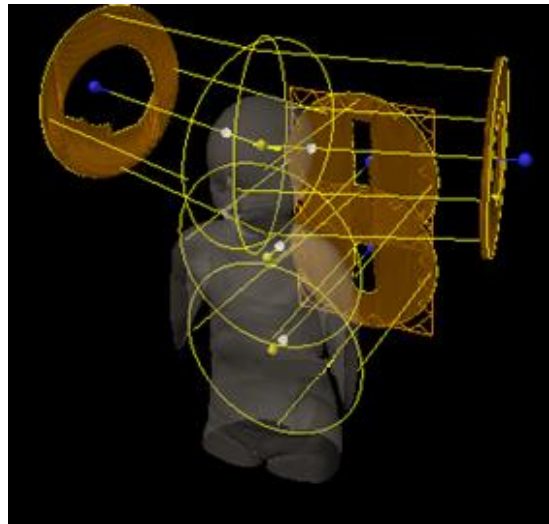

Field setup: Two posterior spinal fields and two oblique cranial fields

- Well established technique in the management of CNS malignancies

- CSI plans were created on CT images (in prone position) for six patients

- Treatment plans* (similar field configuration):
  – Conformal photons (3DCRT)
  – Electrons and photons combined
  – Double scattering (DS) protons
  – Intensity-modulated proton therapy (IMPT)

- Standard risk medulloblastoma: 23.4 Gy(RBE) to brain and spine

- Vertebrae included in target volume for proton plans

*Eclipse, Varian Medical Systems, Palo Alto, CA, USA

Secondary Cancer Risk Analysis

- Risk of radiation-induced cancer for organs either in or near the spinal fields

- To cover a range of possible dose-risk relationships, we included:

    – Linear dose-response
    – Plateau response above 4.5 Gy [Hall, 2003]
    – Organ specific linear-exponential response obtained from fit to Hodgkin's patient statistics [Schneider, 2005]

- Organ equivalent dose (OED) concept: a dose-volume distribution can be converted into a single measure (in units of Gy) representing risk imposed by an equivalent uniform dose – can be compared directly

- Lifetime attributable risk (LAR) - for absolute risk estimates the preferred models for age- and gender- dependent site-specific solid cancer from the BEIR* VII report has been used in combination with the dose-response models

*Board on Biological Effects of Ionizing Radiation, 2006
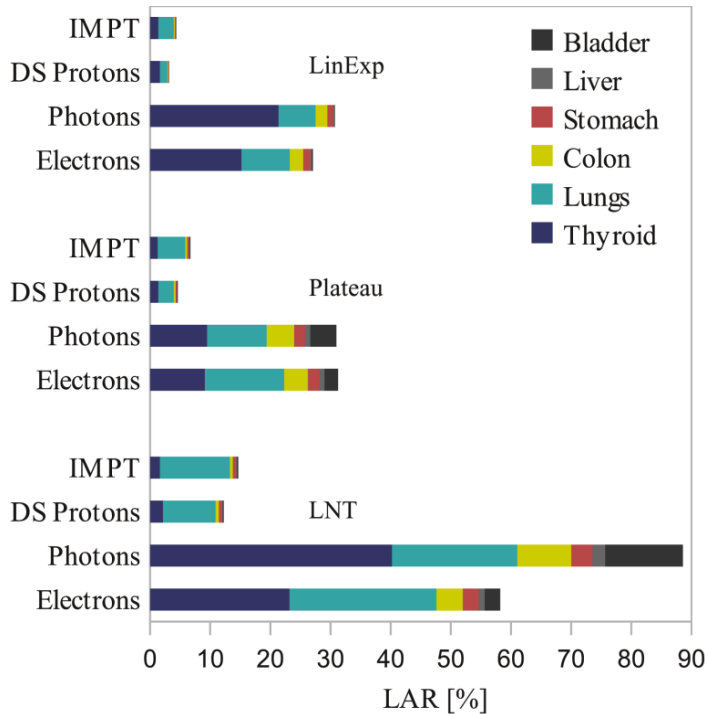
Dose-volume distributions
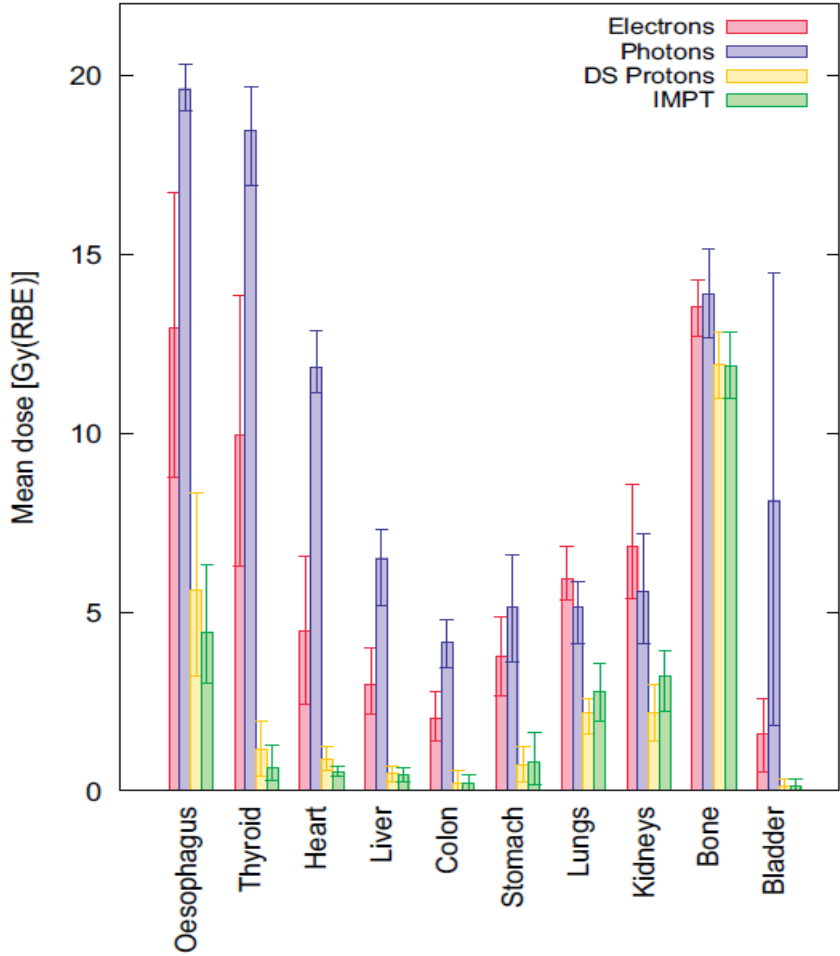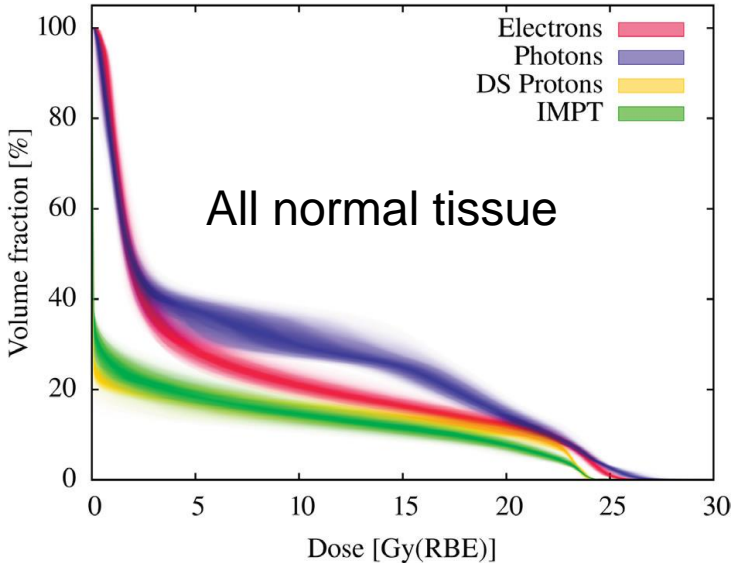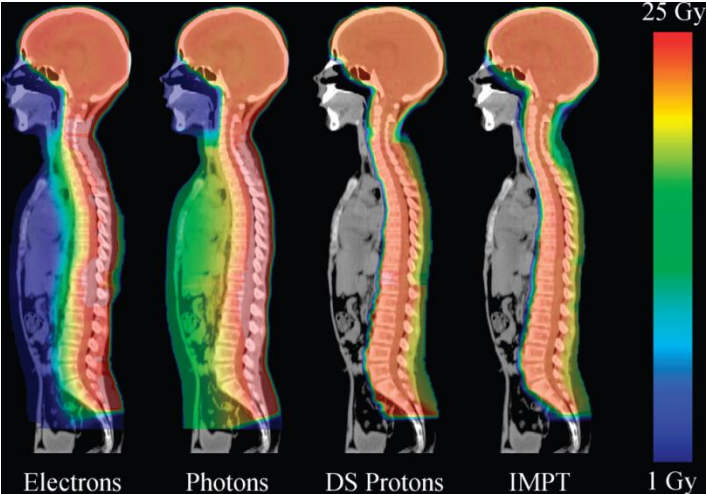
OED and lifetime attributable risk
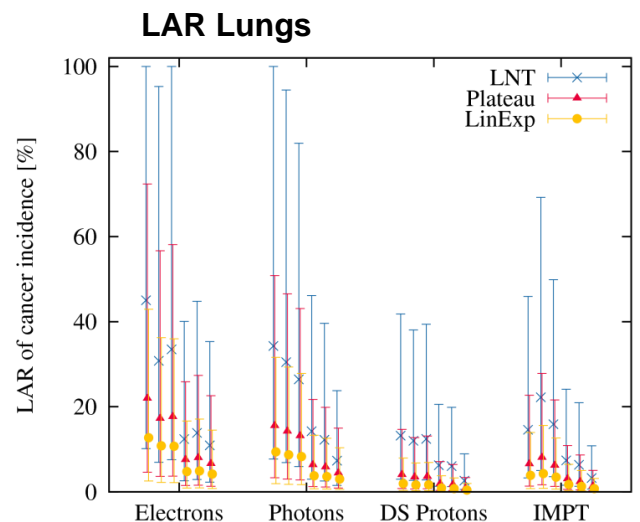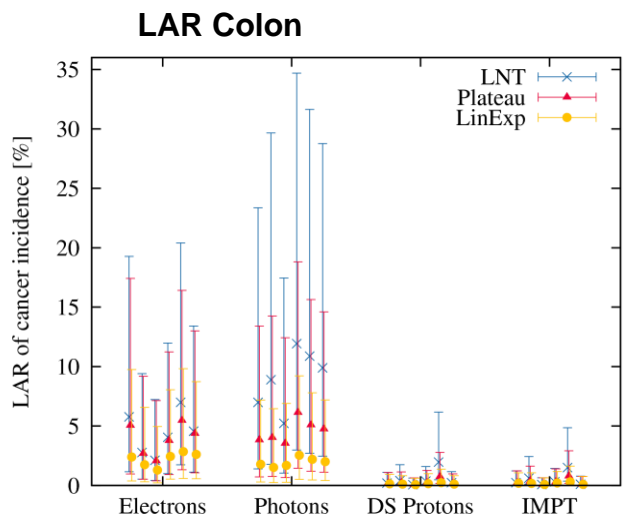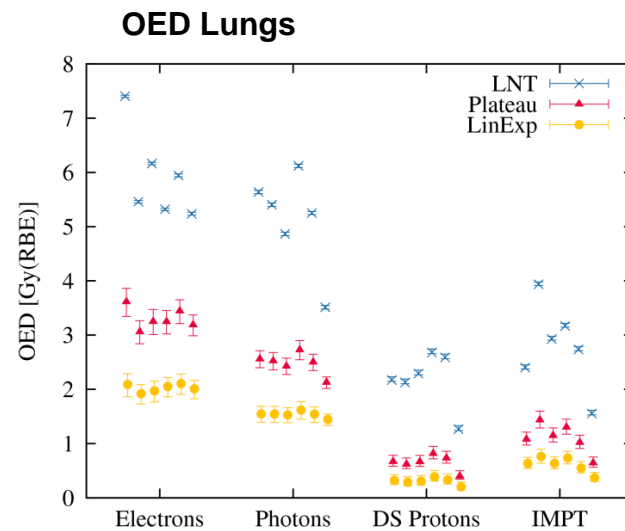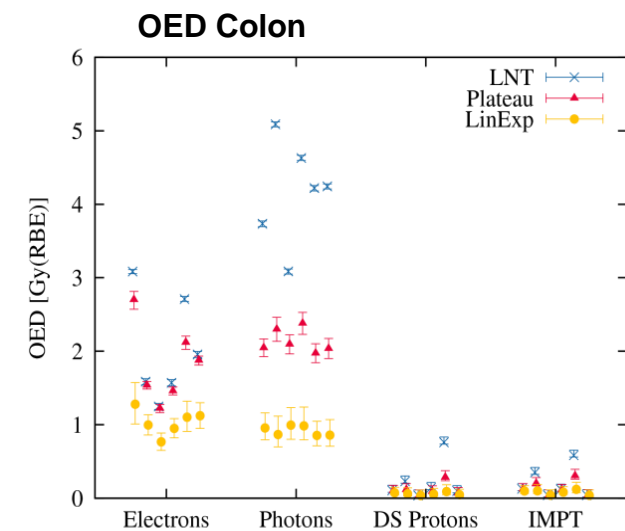
Patient sequence from left to right: female: 5 y ,7y, 8y, male: 8y, 8y, 11y. [95% CI]

Organ-specific lifetime attributable risk

Lifetime attributable risk of cancer incidence for six paediatric CSI patients stratified by technique. (weighted 2:1 for male:female)
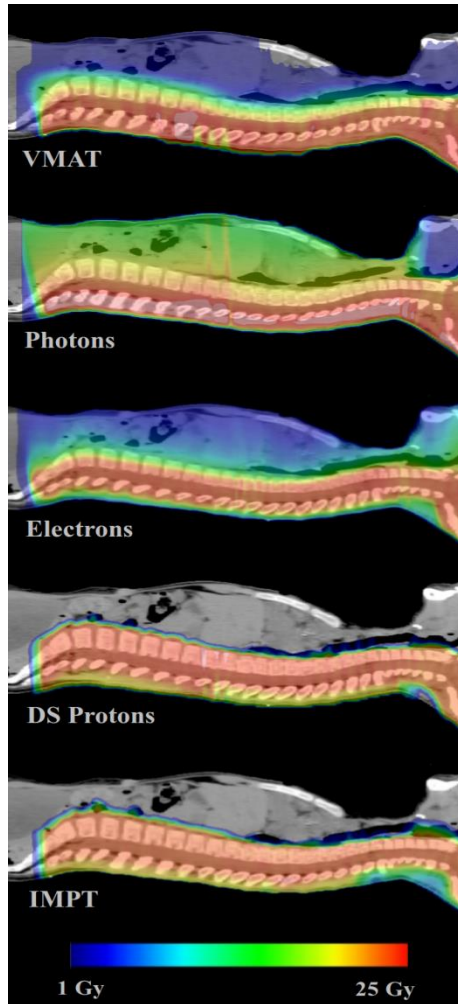
- Stacked organ-specific LARs were about six times higher for the conventional photons and electrons compared to the proton techniques

- The lungs and the thyroid contributed the most to the total risk from all techniques in the patient population

Difference between female and male patients (linear-exp. model)

CSI dose distributions for 8 year old female patient
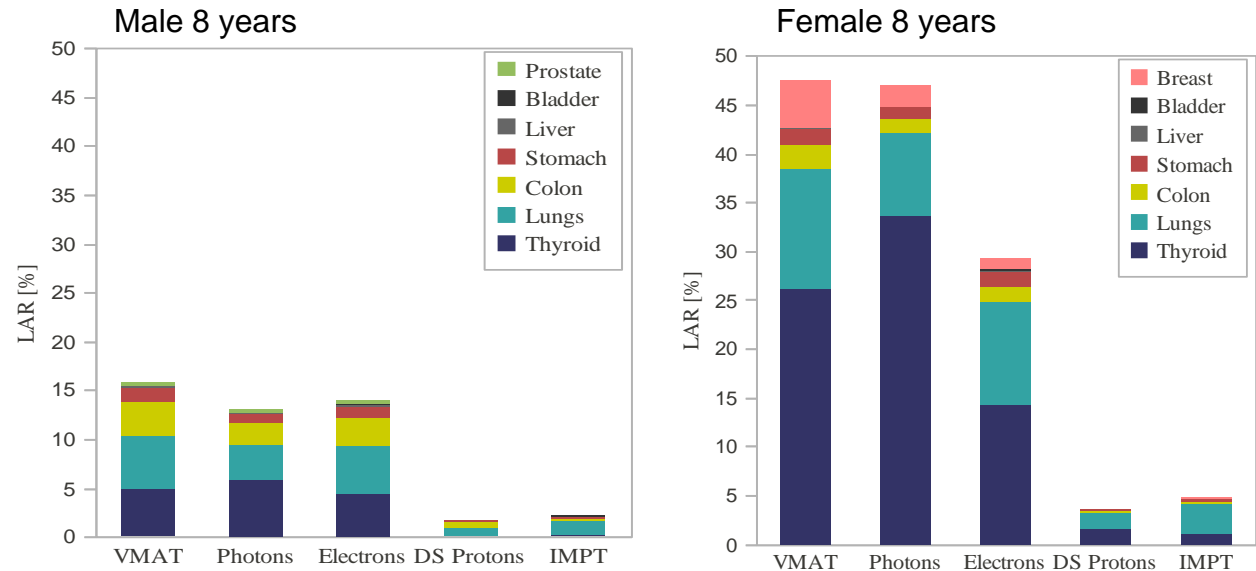
- Higher risks for the female patient relative to the male patient, much due to the higher susceptibility for female thyroid and lung cancer

- For this female patient, the lifetime attributable risk were 13 times higher with both photon techniques compared to the proton techniques

- Reduced doses to the thyroid by using electrons contributes to reduced lifetime attributable risk for the female patient

Conclusions

- Across all models applied, there was a clear reduction in secondary cancer risk when using protons

- Considering the spectrum of risk responses, the differences between the DS protons and IMPT were small, comparable to the difference between the photon and electron techniques

- Large uncertainties in the lifetime attributable risk support the use of OED when comparing risks from alternative treatment plans

Risk of radiation-induced secondary rectal and bladder cancer following radiotherapy of prostate cancer

Camilla H Stokkevåg[1,2], Grete-May Engeseth[1],
Liv B Hysing[1], Kristian S Ytre-Hauge[2], Christian Ekanger[1], Ludvig P Muren[3]

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[2] Department of Physics and Technology, University of Bergen, Norway
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Introduction

- Secondary cancer risks rising to as high as 1 in 70 have been observed in prostate cancer patients after treatment with older radiotherapy techniques (10+ years follow-up)

- The majority (about 2/3) of the secondary cancers after radiotherapy of prostate cancer are located in directly irradiated tissues (such as the bladder and rectum)

Aims

- Estimate secondary cancer risks for the bladder and rectum following radiotherapy from a previously applied technique (CRT) as well as volumetric arc therapy (VMAT) and intensity modulated proton therapy (IMPT)

- Match the estimated risk from CRT to follow-up data

- Use a wide range of dose-response models

Radiotherapy of localised prostate cancer

- Treatment plans were generated on CT scans for 10 prostate cancer patients. Primary clinical target volume (CTV) included the prostate gland and the seminal vesicles

- The **CRT** plans were generated using wide margins assuming patient positioning by bone matching. 15 mm CTV expansion (10 mm posteriorly)

- **VMAT** and **IMPT** were simultaneously integrated boost plans with narrow margins (5 mm) assuming image-guidance with prostate fiducials. 67.5 Gy to the prostate and 60 Gy to the seminal vesicles (Stray dose IMPT estimated from Fontenot et al. 2010)
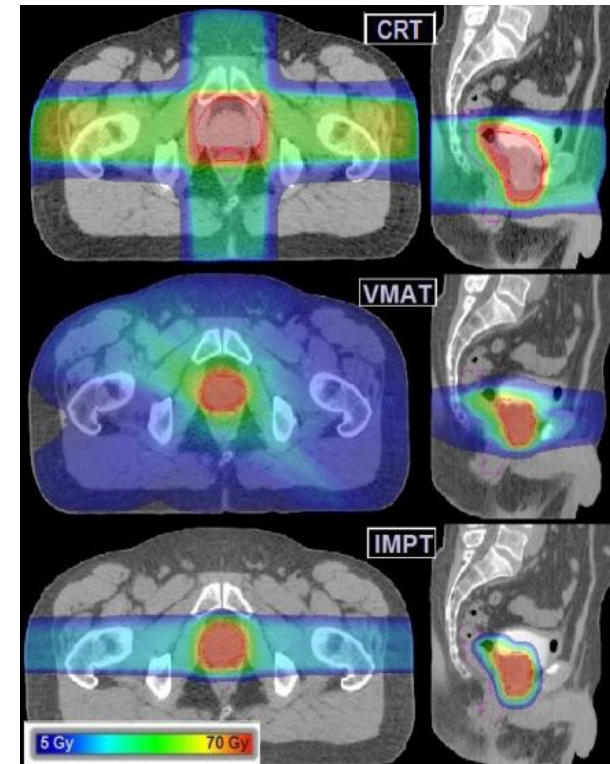
CRT/VMAT: 5-70 Gy and IMPT: 5-70 Gy(RBE)
(Eclipse, Varian)

Dose prescription		
		Target dose in Gy(IsoE)*
	Dose prescription	(Corresponding 2 Gy fr.)
CRT	70 Gy /35 fr.	70 Gy
VMAT	67.5 Gy /25 fr.	79.5 Gy
IMPT	67.5 Gy(RBE) / 25 fr.	79.5 Gy
* Calculated using α/β=1.93 from Vogelius et al. 2013		

Secondary Cancer Risk Analysis

- DVHs for the bladder and rectum for each individual patient and treatment technique were analysed using the OED concept

- Lifetime attributable risks including age-, gender- and site- specific risk coefficients as estimated by Berrington de Gonzalez et al. 2012, based on BEIR VII committee models

<u>Dose-response relationships included</u>:
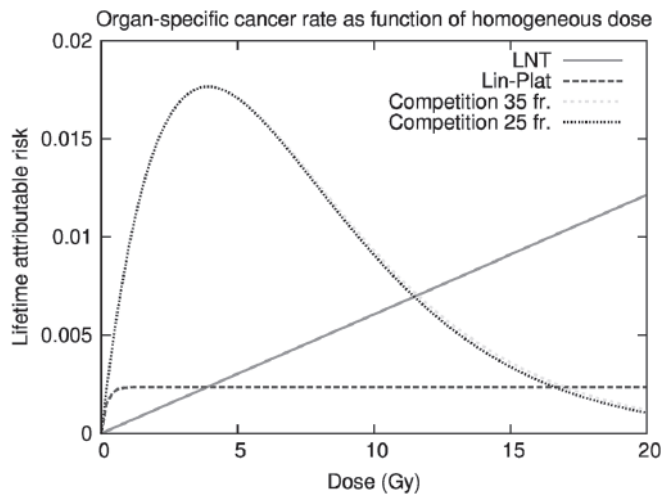
Linear-no-threshold (LNT) dose-response from atomic bomb survivors adjusted by a reduction ratio estimated in a systematic review of dose-response relationships in radiotherapy (Berrington de Gonzalez et al. 2013)

Linear-plateau (Lin-Plat) relationship with organ-specific parameters from fit to Hodgkin's patients follow-up data (Schneider and Kaser-Hotz. 2005)

Bell-shaped (competition) model with reduction in risk at higher doses with incorporated effects of fractionation (Daşu et al. 2005)

Organ-specific cancer rate as function of homogeneous dose
- LNT
- Lin-Plat
- Competition 35 fr.
- Competition 25 fr.

x-axis: Dose (Gy)
y-axis: Lifetime attributable risk

Variations between patients
- risk estimates for the bladder

- Degree of fluctuation varied between patients depending on applied model and radiotherapy technique

- Strong inter-patient variations
  - High LNT risk was patient specific with techniques ranked in same sequence
  - Competition model estimates varied more across techniques

- In general the risk estimates for the rectum varied less than for the bladder

Linear-no-threshold

Competition/bell-shaped

■ IMPT ◆ VMAT ▲ CRT   **Age 60 years**
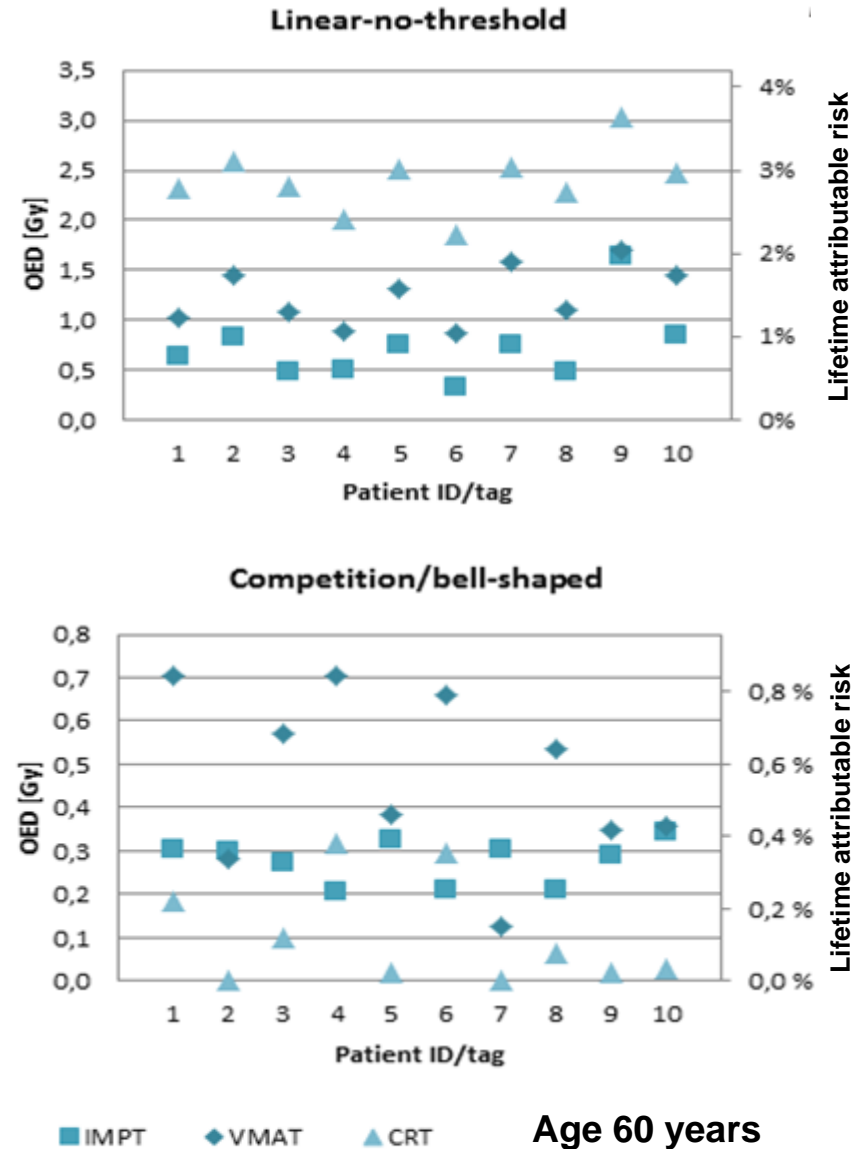
Lifetime attributable risk if exposed at age 60 years
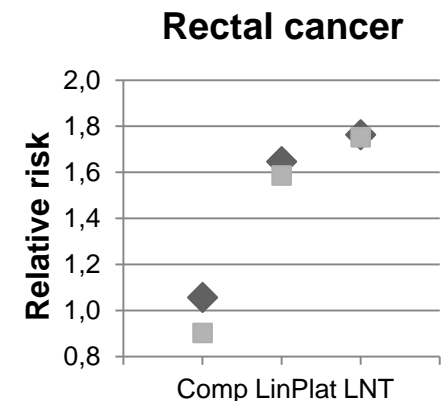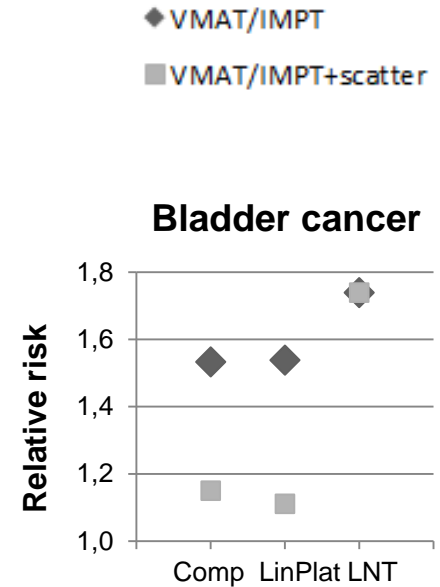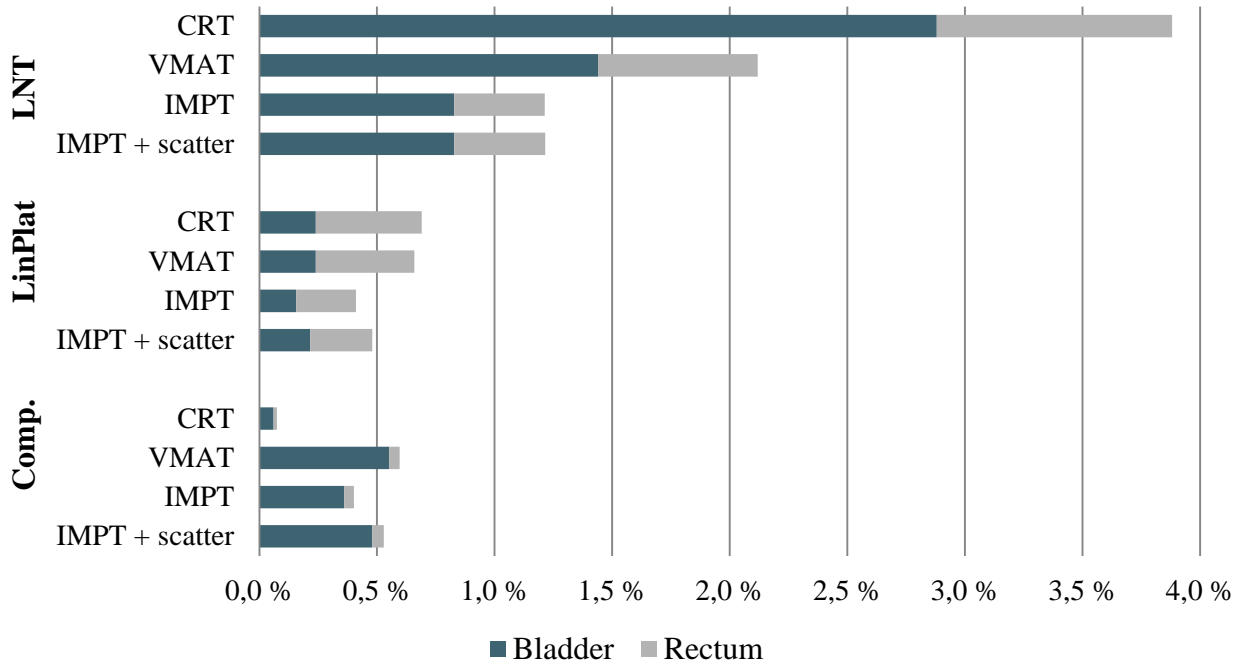
- **CRT** was assigned the lowest risk by the competition model and the highest risk by the linear model

- **VMAT vs. IMPT**
  - Estimated risk of **bladder** cancer was higher for VMAT:
    - 1.1-1.7 times the risk of IMPT
  - Risks of **rectal** cancer
    - 0.9-1.7 times the risk of IMPT

Risk of bladder and rectal cancer

LAR range assuming age at exposure 60 years				
	Bladder cancer			
	CRT	VMAT	IMPT	IMPT + scatter dose
LAR Comp	0.0-0.4%	0.2-0.8%	0.3-0.4%	0.4-0.5%
LAR LinPlat	0.2-0.2%	0.2-0.2%	0.1-0.2%	0.2-0.2%
LAR LNT	2.2-3.6%	1.0-2.0%	0.4-2.0%	0.4-2.0%
	Rectal cancer			
	CRT	VMAT	IMPT	IMPT + scatter dose
LAR Comp	0.00-0.03%	0.01-0.06%	0.03-0.05%	0.04-0.05%
LAR LinPlat	0.4-0.5%	0.4-0.5%	0.2-0.3%	0.2-0.4%
LAR LNT	0.9-1.3%	0.6-1.0%	0.2-0.6%	0.3-0.6%

- Clinically reported risks of bladder cancer 0.5-0.6%
  [Brenner et al. Cancer 2000, Singh et al. Int J Radiat Oncol Biol Phys 2010]

- Rectal cancers reported following RT 0.1-0.2%
  [Baxter et al. Gastroenterology. 2005, Brenner et al. Cancer 2000]

Risk of bladder and rectal cancer

LAR range assuming age at exposure 60 years				
	Bladder cancer			
	CRT	VMAT	IMPT	IMPT + scatter dose
LAR Comp	0.0-0.4%	0.2-0.8%	0.3-0.4%	0.4-0.5%
LAR LinPlat	0.2-0.2%	0.2-0.2%	0.1-0.2%	0.2-0.2%
LAR LNT	2.2-3.6%	1.0-2.0%	0.4-2.0%	0.4-2.0%
	Rectal cancer			
	CRT	VMAT	IMPT	IMPT + scatter dose
LAR Comp	0.00-0.03%	0.01-0.06%	0.03-0.05%	0.04-0.05%
LAR LinPlat	0.4-0.5%	0.4-0.5%	0.2-0.3%	0.2-0.4%
LAR LNT	0.9-1.3%	0.6-1.0%	0.2-0.6%	0.3-0.6%

- Clinically reported risks of bladder cancer 0.5-0.6%
  [Brenner et al. Cancer 2000, Singh et al. Int J Radiat Oncol Biol Phys 2010]

- Rectal cancers reported following RT 0.1-0.2%
  [Baxter et al. Gastroenterology. 2005, Brenner et al. Cancer 2000]

Conclusions

- The relative relationship of secondary cancer risk between the contemporary techniques and CRT depended on the choice of model

- The estimated secondary cancer risks for the bladder and rectum for IMPT were lower or comparable to VMAT - no clear advantage

The influence of inter-fractional anatomy variation on model-based secondary cancer risk estimates following radiotherapy of prostate cancer with photons and protons

Camilla H Stokkevåg[1,2], Grete-May Engeseth[1],
Liv B Hysing[1], Kristian S Ytre-Hauge[2], Ludvig P Muren[3]

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Manuscript in preparation

Introduction

- The rectum and bladder are highly mobile structures which can result in considerable variation in dose received during radiotherapy

Aims

- Investigate how inter-fraction motion would influence model estimates

- Investigate whether a "patient-specific" risk could be found in spite of anatomy variation

Materials and methods
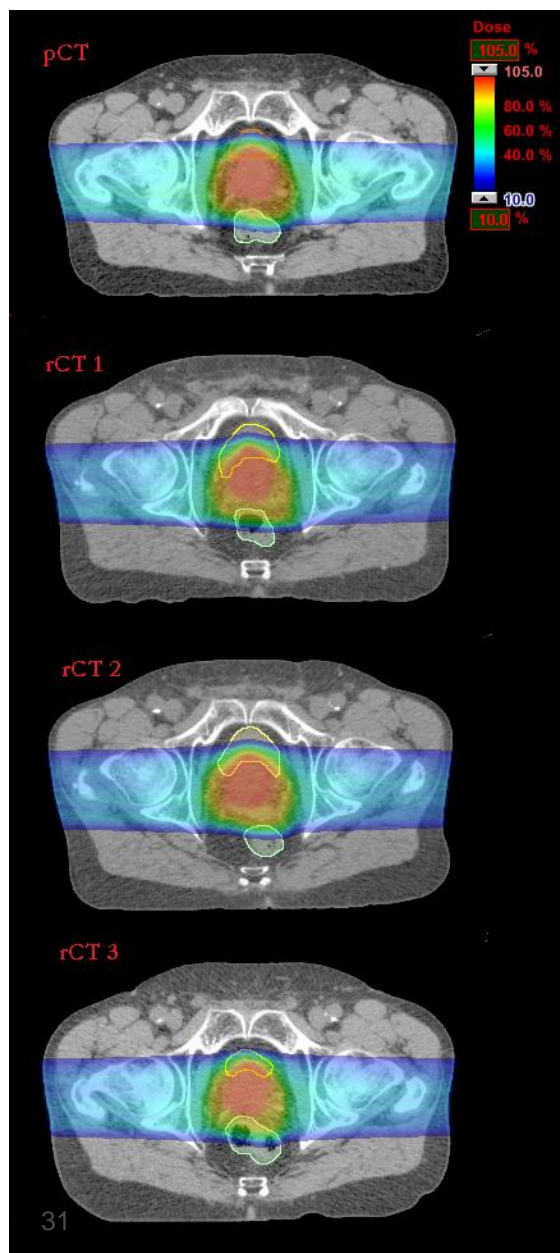
- Each patient had 8-9 repeat CT (rCT) scans throughout the course of treatment on which the bladder and rectum were re-contoured and the originally planned dose distribution re-calculated assuming fiducial marker based image-guidance

- Relative risk of radiation-induced cancer (VMAT/IMPT) were calculated from the planned and re-calculated dose distributions using the linear and the competition model

- Two-factor ANOVA without replication was used to assess the variation between individual patient-specific RR based on the rCTs. Intraclass correlation (ICC) estimated for patient-specific rCTs against all rCTs and pCTs
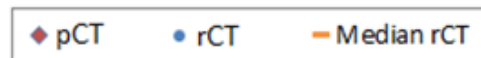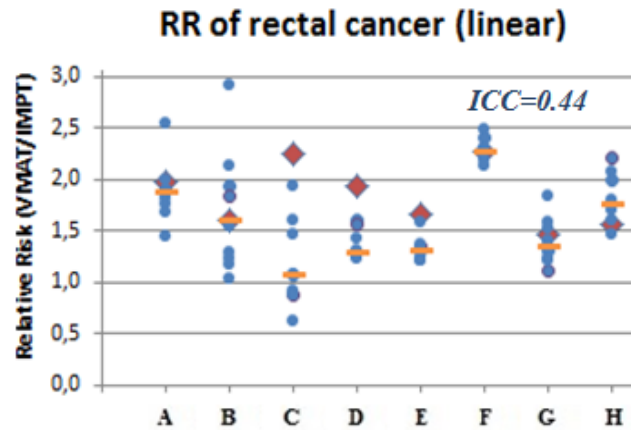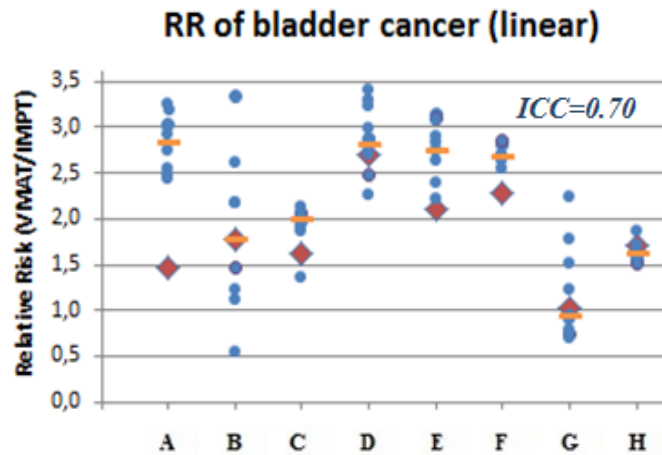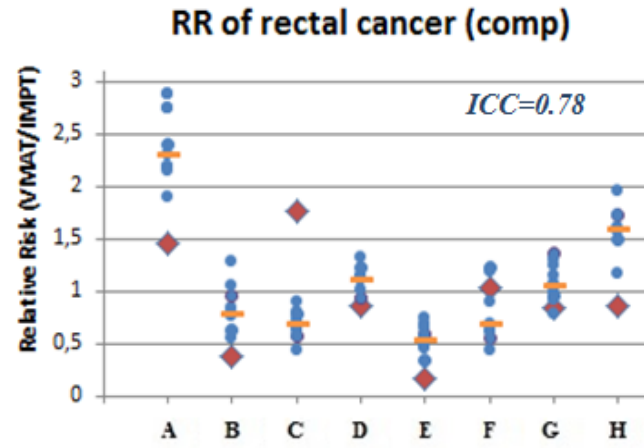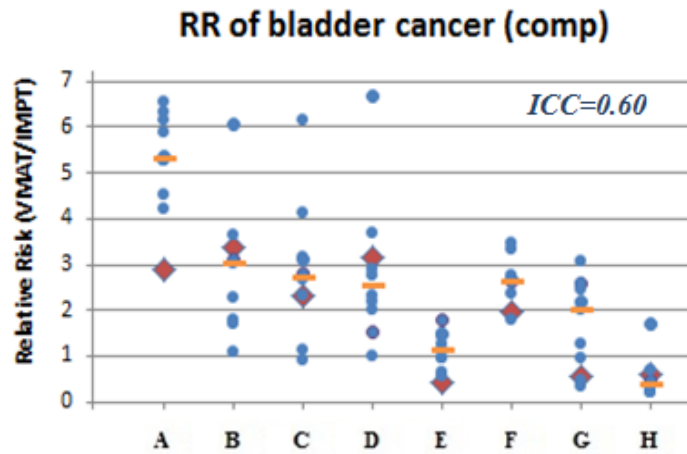
ICC=0: no correlation between rCTs for each patient
ICC=1: perfect correlation between rCTs for each patient

Conclusions

- Day-to-day variation in the RRs across rCTs were in the same range as the inter-patient variations and makes it challenging to predict patient specific secondary cancer risk based on one pCT only

- Considerable difference in RR between patients also when taking organ motion into account, indicating that the secondary cancer risks are indeed patient specific

- In secondary cancer risk modelling, multiple patients or rCT scans should be included for prostate cancer patients where organ motion has a significant impact

Modelling of organ-specific radiation-induced secondary cancer risks following particle therapy

Camilla H Stokkevåg[1,2], Mai Fukahori[3,] Takuma Nomiya[3,4], Naruhiro Matsufuji[3], Grete May Engeseth[1], Kristian S Ytre-Hauge[2], Liv B Hysing[1,2], Artur Szostak[2], Ludvig P Muren[5]

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[3]Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan
[4]Department of Radiation Oncology, Kanagawa Cancer Center, Yokohama, Japan
[5]Department of Medical Physics, Aarhus University / Aarhus University Hospital, Aarhus, Denmark

Introduction

- Role of Carbon(C-)ion therapy in treatment of prostate cancer is under exploration
  - About 2000 prostate patients have been treated with C-ions at the National Institute for Radiological Sciences (NIRS), Chiba, Japan
  - Clinical dose escalation trials

- Currently much uncertainty is associated with carcinogenesis from photon based radiotherapy

- The additional dimension of RBE of protons and C-ions is further less explored for this endpoint

Aim

Estimate and in particular explore relative risks of secondary bladder and rectal cancer after C-ion radiotherapy using an RBE adjusted model

Patient material and dose prescription

- CT-scans from ten patients treated for localised prostate cancer

- Clinically applied treatment protocols for VMAT and C-ions

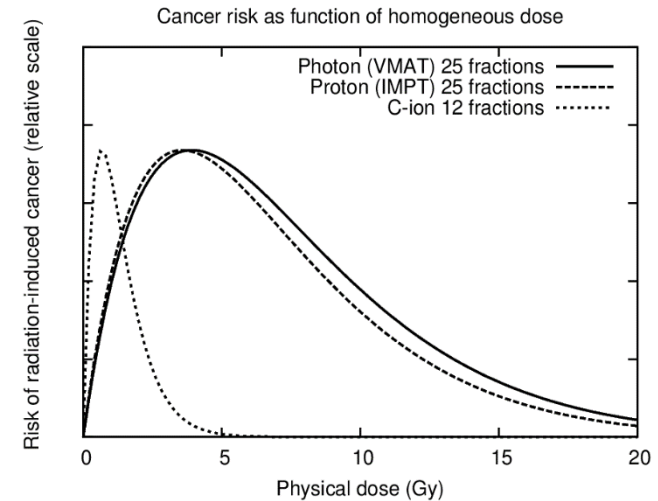| Plan characteristics				
	Dose / fractionation	**Image Guidance**	**Beam configuration**	**Dose optimisation**
VMAT	67.5 Gy / 25 fr.	fiducial markers /keV	6 MV single arc with posterior avoidance sector 12°	Eclipse (Varian)
IMPT	67.5 Gy(RBE) / 25 fr.	fiducial markers /keV	lateral opposing fields	Eclipse (fixed RBE=1.1)
C-ion	51.6 Gy(RBE) / 12 fr.	bone matching* /keV	lateral opposing fields	Modified MKM**, XiO-N (Elekta)
*motion restricted with pelvic body mask **microdosimetric kinetic model [Inaniwa et al. Phys Med Biol, 2010]				

- **VMAT** and **IMPT** were simultaneously integrated boost plans: 67.5 Gy(RBE) to the prostate and 60 Gy to the seminal vesicles. CTV-PTV margins (5 mm)

- Hypo-fractionated **C-ion** (active scanning) One beam delivered per fraction (8 fr. full PTV / 4 fr. boost PTV / 4 times per week)
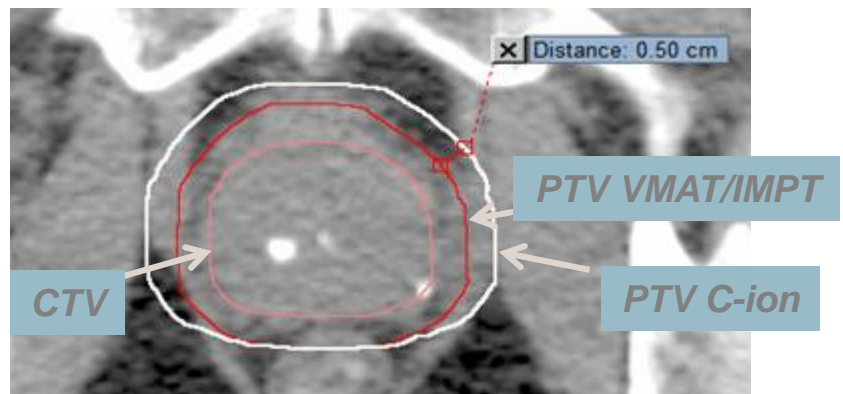
VMAT - Volumetric Arc Therapy
IMPT - Intensity modulated proton therapy

Secondary cancer risk analysis

- RBE-adjusted bell-shaped dose-response model (Jones 2009) extended to whole organs using the OED concept (Schneider 2005)

- The model formulates the RR of secondary cancer by means of low-LET* radio-sensitivity parameters α and β

- For high-LET radiation, RBE_{max} and RBE_{min} are the RBE defined at the low and high dose limit, respectively

Cancer risk as function of homogeneous dose

Risk of radiation-induced cancer (relative scale)

Photon (VMAT) 25 fractions ——
Proton (IMPT) 25 fractions ------
C-ion 12 fractions ·······

Physical dose (Gy)

$$RR = \frac{\int_V n_X(\alpha d_X + \beta d_X{}^2)\, e^{-n_X(\alpha d_X + \beta d_X{}^2)}\, dV}{\int_V n_p\left(RBE_{max}\alpha d_p + RBE_{min}^2\beta d_p{}^2\right) e^{-n_p\left(RBE_{max}\alpha d_p + RBE_{min}^2\beta d_p{}^2\right)} dV}$$

- Parameter scan using the dose distributions of the bladder and rectum
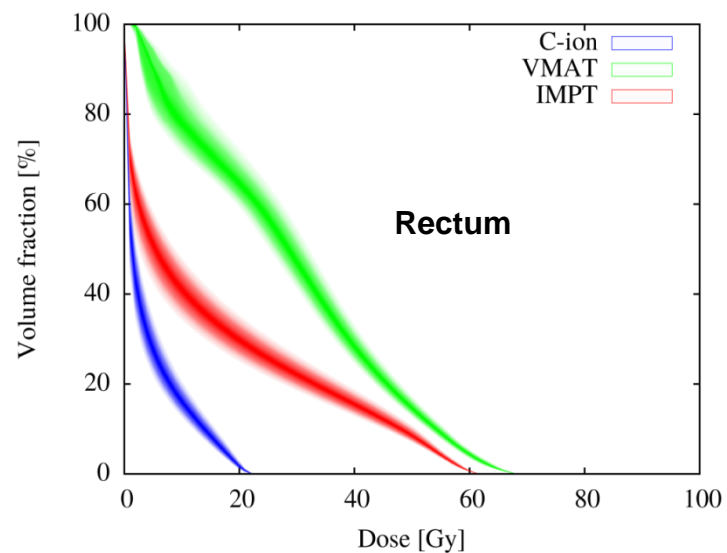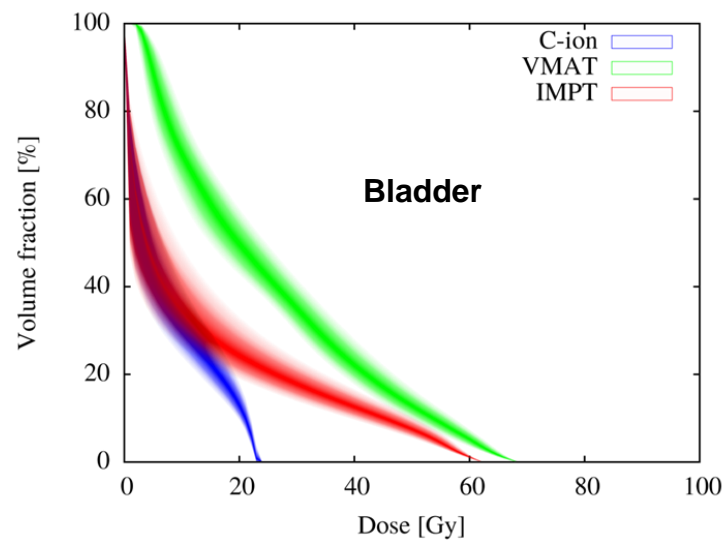- Also included scenario with difference in mutation and cell-inactivation rate of C-ions

*LET = Linear Energy Transfer

Biological (clinical) dose distributions
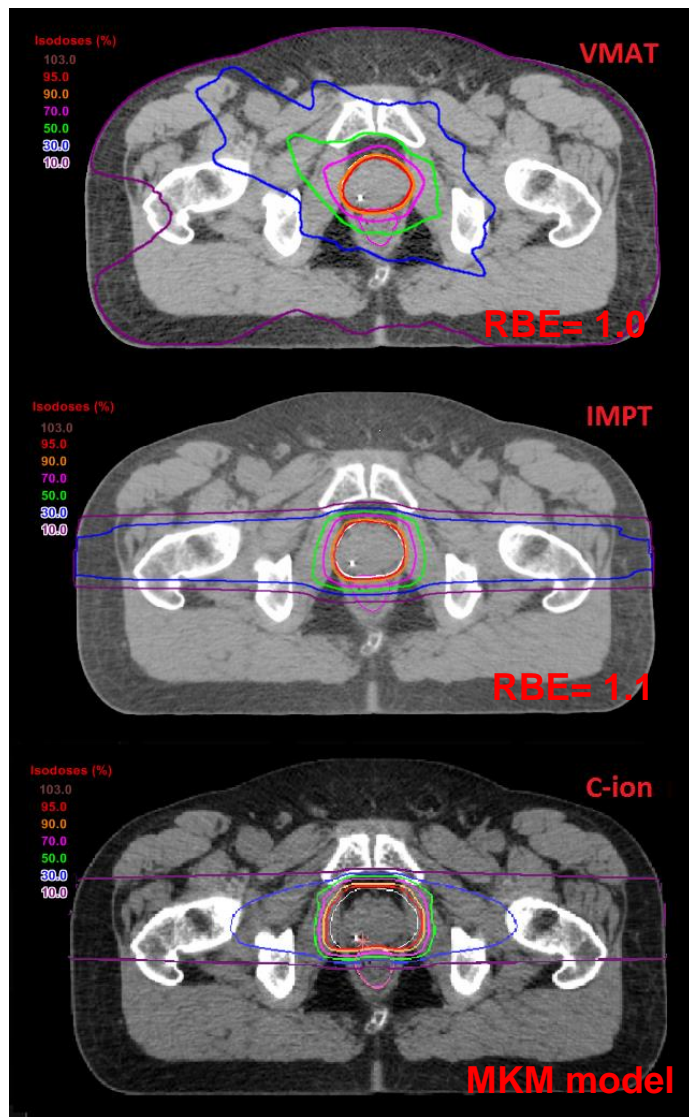
Physical dose volume histograms
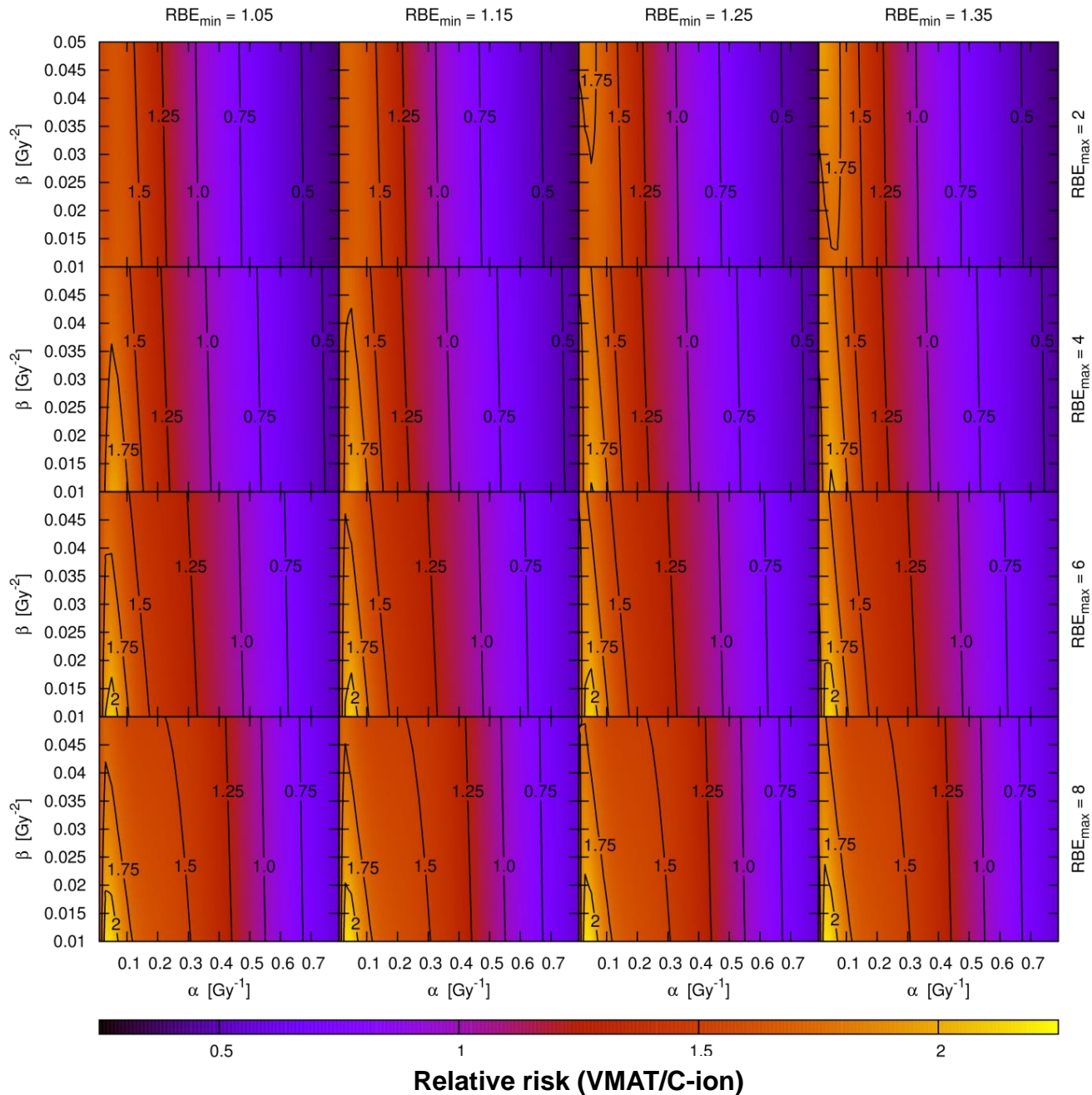
Mean (95% CI) ten patiens

VMAT/C-ion bladder

> Over the scanned ranges the risk could be changed from favouring one technique instead of the other

> Higher α-values increased risk from C-ions

RR>1 means higher risk from VMAT compared to C-ions
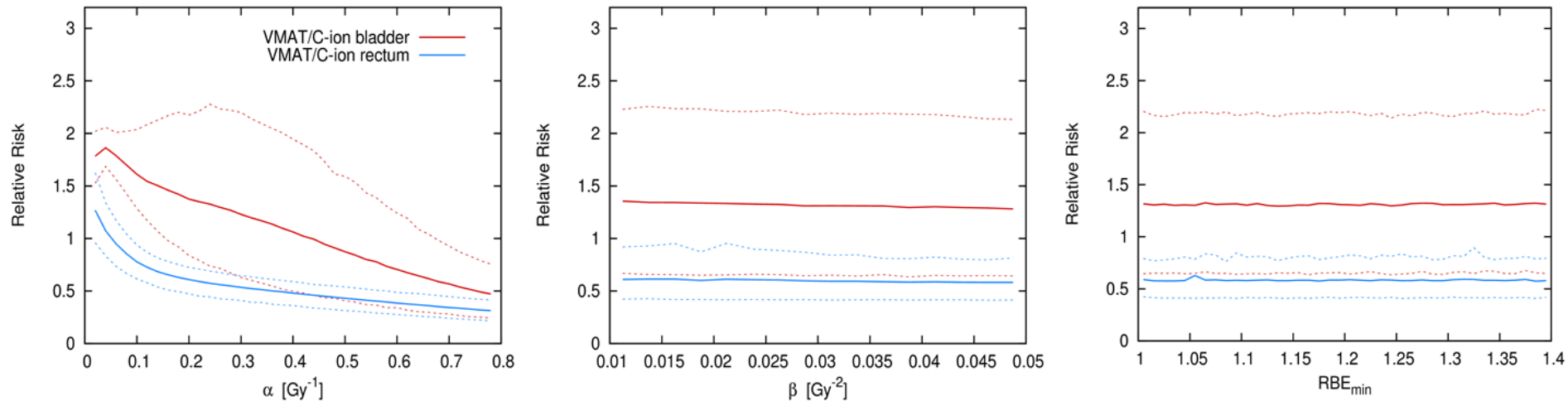
RR<1 means higher risk from C-ions compared to VMAT

40

VMAT/C-ion bladder and rectum - 1D scan (remaining parameters fixed)

Mean (solid lines) and 95% confidence intervals (dotted lines) of all patients based on nominal parameters


| Nominal model parameters and input distributions				
	Bladder	Rectum	Distribution	Ref. nominal value
α (Gy^{-1})	0.25 (σ=0.075)*	0.25 (σ=0.075)*	Gaussian	Daşu et al. Int J Radiat
β (Gy^{-2})	0.033 (σ=0.0055)*	0.046 (σ=0.0077)*	Gaussian	Oncol Biol Phys, 2011
RBE$_{min}$ (C-ion)	1.25 (1.2, 1.3)	1.25 (1.2, 1.3)	Triangle	Jones. J Radiol Prot,
RBE$_{max}$ (C-ion)	6 (5, 7)	6 (5, 7)	Triangle	2009
* percentage σ from Jones 2009				

- The RR for the rectum was consistently lower than the RR for the bladder

- Increasing α decreased the RR

- Little variation with β and RBE$_{min}$

VMAT/C-ion bladder and rectum - 1D scan (remaining parameters fixed)
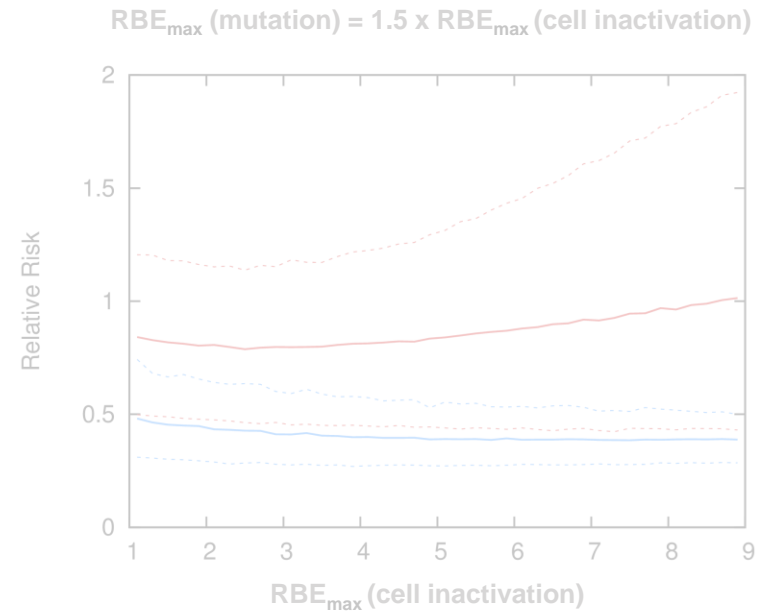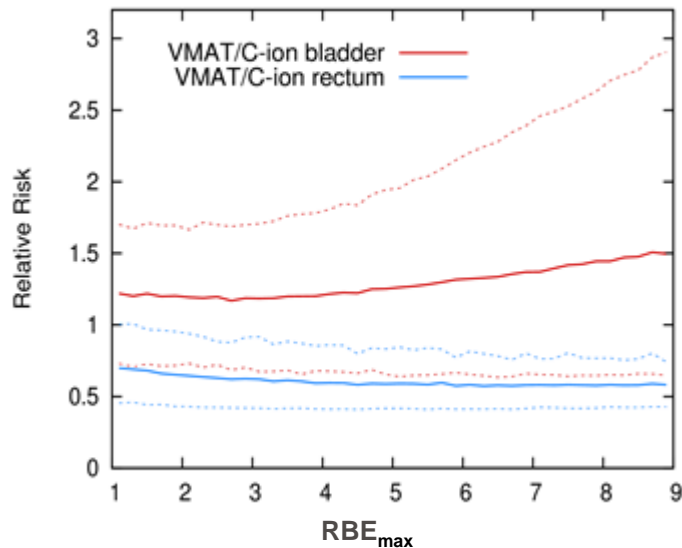
- Considering RBE variations only - the mean RR did not cross over the unity risk boundary (RR=1) for neither the rectum nor bladder

- Increasing the C-ion RBE for cell mutation relative to cell inactivation increased the risk for C-ions

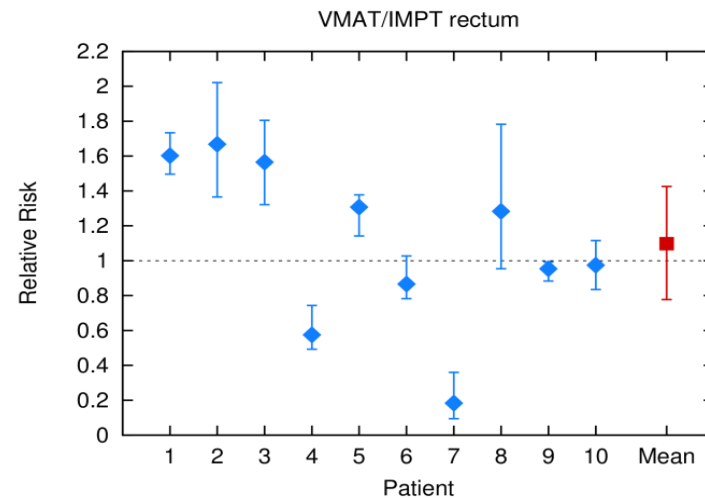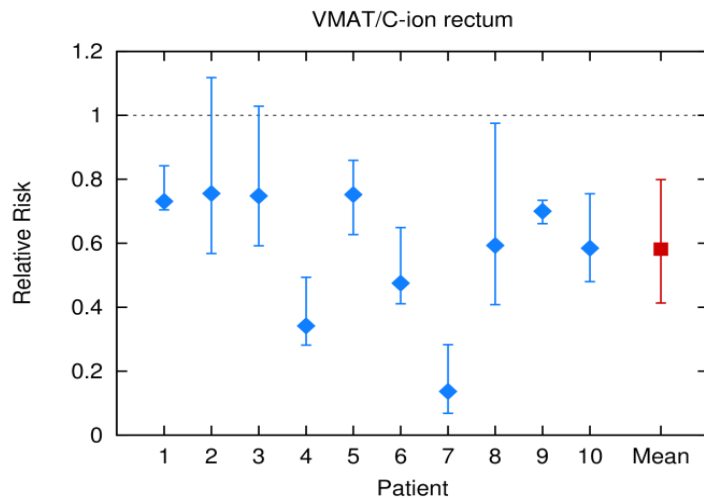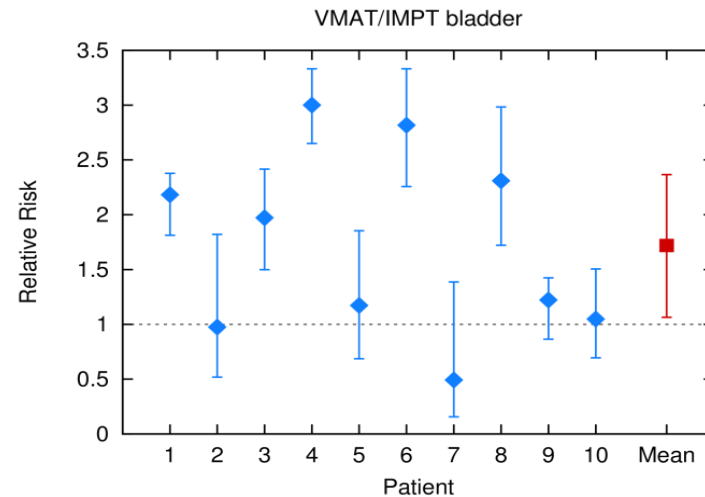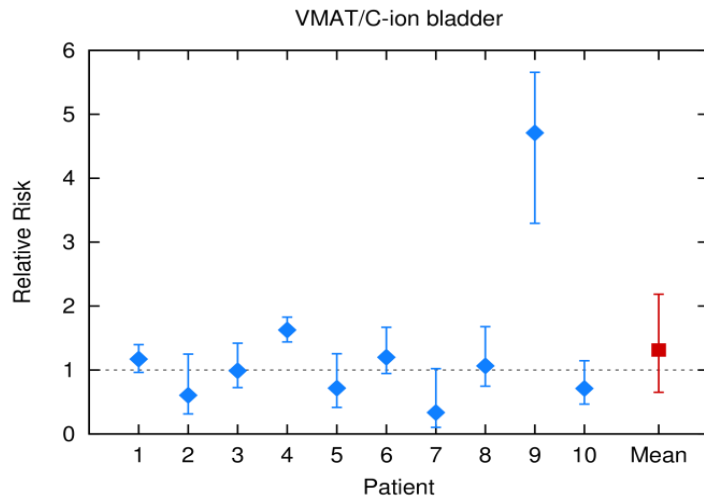# VMAT/C-ion bladder and rectum - 1D scan (remaining parameters fixed)
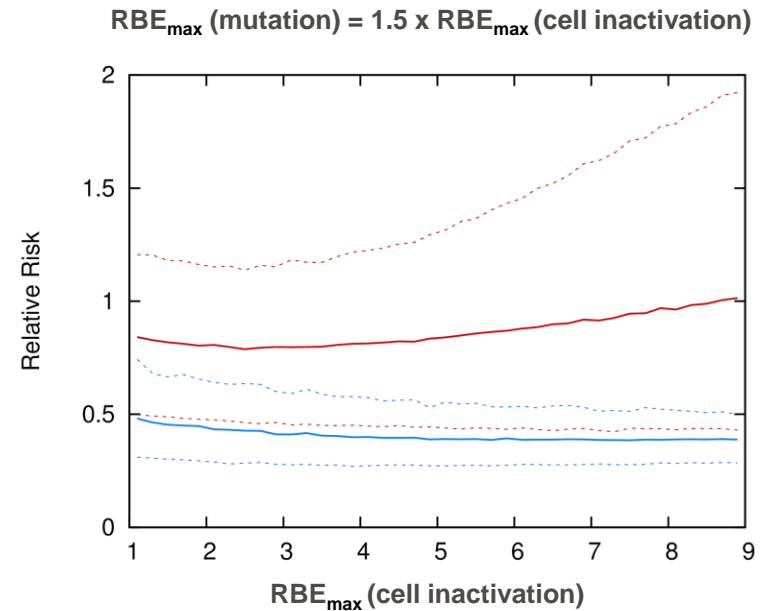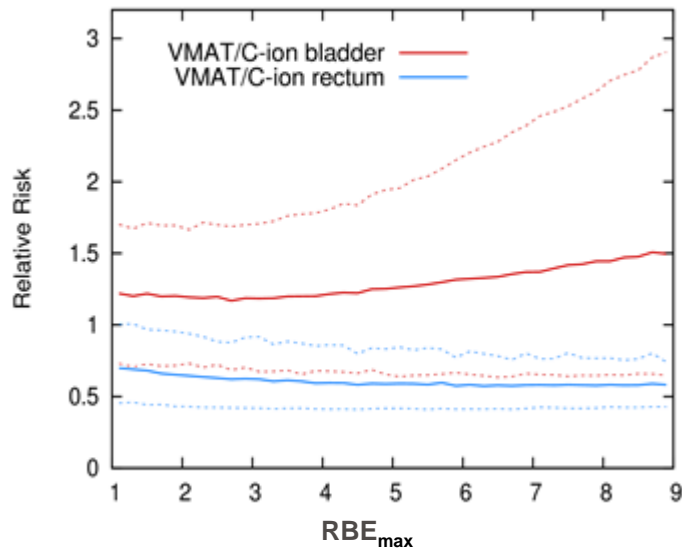
- Considering RBE variations only - the mean RR did not cross over the unity risk boundary (RR=1) for neither the rectum nor bladder

- Increasing the C-ion RBE for cell mutation relative to cell inactivation increased the risk for C-ions

Variation between patients

Relative risks for individual patients based on nominal parameter distributions. Mean of all patients and 95% CI for RBE_{max} (mutation) = RBE_{max} (cell inactivation)

Conclusions

- Based on the wide spread in RR between patients and variations across the included parameter values, the risk profiles of the rectum and bladder were not dramatically different for the investigated radiotherapy techniques

- Estimated RRs were more in favour of protons than Carbon ions, also particles appear to be more beneficial with respect to secondary bladder cancer than secondary rectal cancer

- The radio-sensitivity parameter α had a strong influence on the results with decreasing RR for increasing values of α

- Different RBEs depending on endpoint may also influence RR and should be considered when modelling secondary cancer risks

Further work: LET-inclusive secondary cancer models?
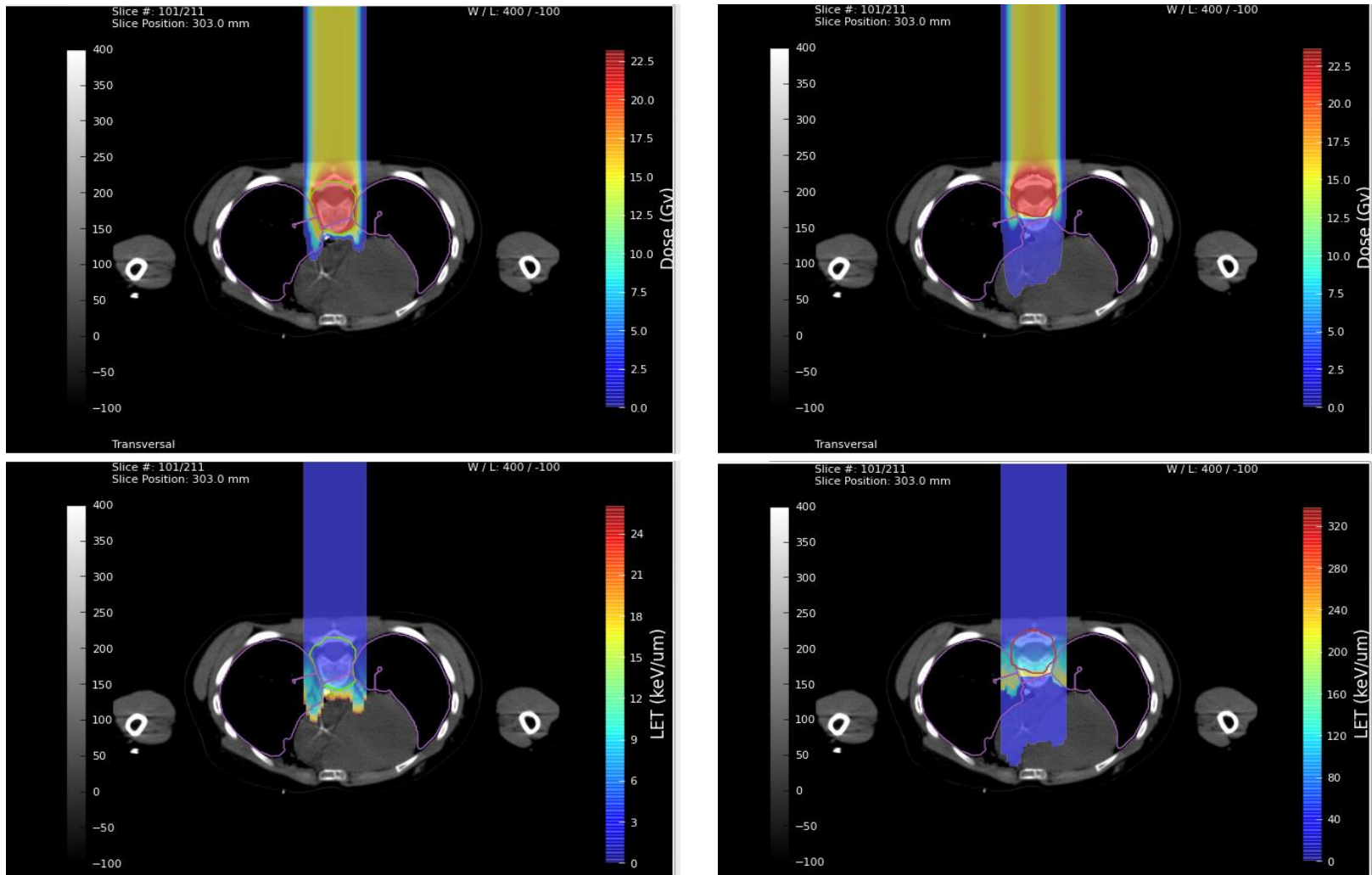
Dose (above) and LET distributions (below) for protons (left) and C-ions (right)

Toussaint et al, 2016 (unpublished)

Overall conclusions

- Despite large confidence intervals, a clear reduction in late effects for paediatric cranio-spinal irradiation if treating with protons was found from the estimates

- For prostate patients, the estimated secondary cancer risk profiles for the bladder and rectum were not dramatically different for the investigated radiotherapy techniques

- Scanning through a wide range of RBE values resulted in only minor differences in ranking between carbon ions compared to VMAT

- Applying different RBEs for cell mutation and cell inactivation were explored, showing increased risk from carbon ions

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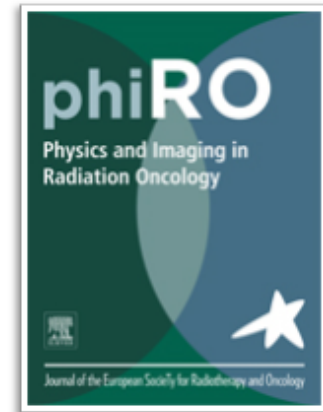
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