Relative risk of radiation-induced malignancy following particle therapy

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Radiation-induced secondary malignancy following particle therapy

- Radiation-induced cancer is a serious late effect following radiotherapy

- With the rapid developments in radiotherapy there is an increasing need for outcome prediction models for late effects of new treatment techniques

- Currently much uncertainty is associated with carcinogenesis from photon based radiotherapy, and the uncertainty is even higher for particle therapy

The aim of this work was to estimate and explore relative risks (RR) of secondary bladder and rectal cancer from photon, proton and C-ion therapy as applied in clinical practice of RT of prostate cancer
Prostate cancer

- Secondary cancers (SC) rising to as high as 1 in 70 have been observed in patients after prostate cancer based on more than ten years follow-up after treatment with older RT techniques.

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

References:
Murray et al. Radiother Oncol 2014
Baxter et al. J Radiol Prot 2005
Davis et al. Cancer 2014
Nomiyama et al. Br J C 2014
Patient specifics and dose prescription

CT-scans from ten patients treated for localised prostate cancer at Haukeland University Hospital (HUH), Bergen. Clinical target volume (CTV) included the prostate gland and the seminal vesicles.

<table>
<thead>
<tr>
<th>Treatment planning</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose / fractionation</strong></td>
</tr>
<tr>
<td>VMAT 67.5 Gy / 25 fr.</td>
</tr>
<tr>
<td>IMPT 67.5 Gy(RBE) / 25 fr.</td>
</tr>
<tr>
<td>C-ion 51.6 Gy(RBE) / 12 fr.</td>
</tr>
</tbody>
</table>

*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 to the prostate and 60 Gy to the seminal vesicles. CTV-PTV margins (5 mm)

- Hypo-fractionated **C-ion** (active scanning) One side delivered per fraction (8 fr. full PTV / 4 fr. boost PTV / 4 times per week)
Secondary Cancer Risk Analysis


- The model formulates the RR of malignant induction between VMAT/proton and VMAT/C-ion, expressed by means of low-LET* radio-sensitivity parameters \( \alpha \) and \( \beta \). For high-LET radiation, corrections were incorporated with the parameters \( RBE_{\text{max}} \) and \( RBE_{\text{min}} \), which are the RBE defined at the low and high dose limit, respectively.

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

- We performed a parameter scan using the bladder and rectum dose distributions, where we calculated the mean RR for all patients over different possible combinations of \( RBE_{\text{max}} \), \( RBE_{\text{min}} \), \( \alpha \) and \( \beta \).

*LET = Linear Energy Transfer
Results

Biological dose distributions

Physical dose distributions

Bladder

Rectum
Overall results – based on selected parameters – all ten patients

<table>
<thead>
<tr>
<th>Relative risk</th>
<th>Bladder</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>RR</td>
</tr>
<tr>
<td>VMAT / IMPT</td>
<td>1.72 (95% CI 1.06-2.37)</td>
<td>1.10 (95% CI 0.78-1.43)</td>
</tr>
<tr>
<td>VMAT / C-ion</td>
<td>1.31 (95% CI 0.65-2.18)</td>
<td>0.58 (95% CI 0.41-0.80)</td>
</tr>
</tbody>
</table>

Nominal model parameters and input distributions

<table>
<thead>
<tr>
<th></th>
<th>Bladder</th>
<th>Rectum</th>
<th>Distribution</th>
<th>Ref. nominal value</th>
</tr>
</thead>
<tbody>
<tr>
<td>α (Gy⁻¹)</td>
<td>0.25 (σ=0.075)*</td>
<td>0.25 (σ=0.075)*</td>
<td>Gaussian</td>
<td>Dašu et al. Int J Radiat Oncol Biol Phys, 2011</td>
</tr>
<tr>
<td>β (Gy⁻²)</td>
<td>0.033 (σ=0.0055)*</td>
<td>0.046 (σ=0.0077)*</td>
<td>Gaussian</td>
<td></td>
</tr>
<tr>
<td>RBEₘₐₓ (C-ion)</td>
<td>1.25 (1.2, 1.3)</td>
<td>1.25 (1.2, 1.3)</td>
<td>Triangle</td>
<td></td>
</tr>
<tr>
<td>RBEₘₐₓ (C-ion)</td>
<td>6 (5, 7)</td>
<td>6 (5, 7)</td>
<td>Triangle</td>
<td></td>
</tr>
<tr>
<td>RBEₘₐₓ (proton)</td>
<td>1.03 (1.01, 1.05)</td>
<td>1.03 (1.01, 1.05)</td>
<td>Triangle</td>
<td></td>
</tr>
<tr>
<td>RBEₘₐₓ (proton)</td>
<td>1.25 (1.2, 1.3)</td>
<td>1.25 (1.2, 1.3)</td>
<td>Triangle</td>
<td></td>
</tr>
</tbody>
</table>

* percentage σ from Jones 2009

For reference – follow up from older techniques

- Clinically reported risks of bladder cancer 0.5-0.6%
- Rectal cancers reported following RT 0.1-0.2%
VMAT/C-ion bladder

- Over the scanned ranges the RRs varied and changed the risk in favour of one technique instead of another
- Higher $\alpha$-values increases risk from C-ions
- Higher $RBE_{\text{max}}$ decreases risk from C-ions
- $\beta$ and $RBE_{\text{min}}$ did not influence the RR much

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

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

Variation between patients

Relative risks for individual patients based on nominal parameters. Mean of all patients and 95% CI
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.

- RR estimates were more in favour of protons than C-ions, also particles appear to be more beneficial with respect to secondary bladder cancer than secondary rectal cancer.

- The radio-sensitivity parameter $\alpha$ had a strong influence on the results with decreasing RR for increasing values of $\alpha$. 
Thank you

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Results

Relative risk - RBE end-points

- We also investigated the influence of including a higher C-ion RBE ($RBE_{\text{max}}$) for cell-mutation than for cell-inactivation.

- Data from cell experiments suggests that the C-ion RBE for mutation (cancer induction) is slightly larger than the C-ion RBE for inactivation.

- Such a scenario increased the risk from the C-ions - in worst case results in a threefold higher risk for secondary rectal cancer from C-ions compared to VMAT.

<table>
<thead>
<tr>
<th>End-point dependent RBE mutation vs. inactivation</th>
<th>Bladder</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95 % CI</td>
</tr>
<tr>
<td>VMAT / C-ion 6 vs. 6</td>
<td>1.31</td>
<td>0.65-2.18</td>
</tr>
<tr>
<td>VMAT / C-ion 9 vs. 6</td>
<td>0.88</td>
<td>0.43-1.53</td>
</tr>
<tr>
<td>VMAT / C-ion 12 vs. 6</td>
<td>0.66</td>
<td>0.31-1.15</td>
</tr>
</tbody>
</table>
C-ions more beneficial for the bladder than for the rectum – the RR for the rectum was consistently lower than for the bladder

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

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

Relative risk (RR) VMAT/C-ion parameter scan for the bladder and rectum. Mean (solid lines) and 95% confidence intervals (dotted lines) of all patients based on nominal parameters
Results

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

- Mean RR>1 for both bladder and rectum

RR>1 means higher risk from VMAT compared to IMPT

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

Relative risk (RR) VMAT/IMPT parameter scan for the bladder and rectum. Mean (solid lines) and 95% confidence intervals (dotted lines) of all patients based on nominal parameters.
### VMAT/IMPT bladder

- Same trend as for C-ions, however, with the RR shifted to higher $\alpha$ values
- RR=1 located at $\alpha$-values over 0.6. RR not much influenced from the small variations in $RBE_{\text{max}}$
- $\beta$ and $RBE_{\text{min}}$ did not influence the RR much

RR>1 means higher risk from VMAT compared to IMPT

RR<1 means higher risk from IMPT compared to VMAT