Out-of-field Radiation Risks in Paediatric Proton Therapy

Charlot Vandevoorde
NRF iThemba LABS
Contact: cvandevoorde@tlabs.ac.za

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NRF-iThemba LABS: A national research facility in South Africa

30 years of operations with the Separated Sector Cyclotron (SSC)

Collaboration network with South African universities, institutions and international partners

P(66)/Be neutron therapy unit (29 MeV neutrons): routine treatment started in 1989

Passive double scattering proton therapy (PPT) unit (200 MeV protons): routine treatment started in 1993
Introduction: Clinical advantage of proton therapy (PT) for childhood cancer

Clinical Rationale for PT: Inverted depth dose profile
- Maximum dose at tumour location
- Sparing of surrounding normal tissue

Integral dose is a factor of 2-3 lower for protons compared to photons
- Impact on secondary cancer induction

Children: Higher radiosensitivity and longer life expectancy, resulting in a 2-3 times higher risk for radiation-induced solid tumours and 3-5 times higher risk for radiation-induced leukaemia (UNSCEAR report 2013)

The sparing of normal tissues and the reduction of integral dose makes PT the preferred irradiation technique for treating childhood cancer

Introduction: Stray radiation produced in PT

Dose outside the target volume?
- X-ray based RT (incl. IMRT): predominantly photons scattered in linac head and in patient, but when the energy is high enough neutrons are produced due to photonuclear interactions (above 8-10 MeV)
- PT: primary protons and secondary particles, most importantly neutrons, are inevitably produced through nuclear inelastic reactions with components of the beam line and in patients’ body

Two beam modulation techniques in PT:
- Passive double scattering proton therapy (passive scattering PT)
- Active pencil beam scanning proton therapy (active scanning PT)

“Internal” and “external” neutron production
Introduction: Stray radiation produced in PT

Beam Modulation Technique: **PASSIVE**

![Diagram of passive beam modulation technique]

Majority of neutrons is produced by interaction of high energy protons with material components of beam line, with the largest source of neutrons the collimator close to the patients. Neutron production is dominated by **external neutron component**.

Beam Modulation Technique: **ACTIVE**

![Diagram of active beam modulation technique]

Fewer material components in the beam line, resulting in a lower neutron background than passive PT. Majority of secondary neutron production is generated **internally** in the patient’s body, which is inevitable.
Introduction: Stray radiation produced in PT

The mixed radiation field produced in proton therapy where protons are accelerated to therapeutic energies (60-250 MeV) can be divided into high and low LET components:

**High LET components:** neutrons and charged nuclear fragments (helium ions, deuterons, and tritons)

**Low LET components:** primary protons, elastically scattered protons, photons and delta electrons

In passive PT, the secondary neutron energy spectra are characterized by a low-energy peak (<10 MeV) and a high-energy neutron peak (>10 MeV up to the proton energy), however, the high energy peak contributes most to the total neutron dose. Next to the influence of the beam line configuration, the proton energy will also influence the neutron production as well as the distance from the field edge. The contribution of the low-energy peak increases with out-of-field distance.

Introduction: Impact of neutrons in clinical proton therapy

Neutrons are known to have a high relative biological effectiveness (RBE) and are arguably the most effective particles in inducing late effects. The dosimetric advantage of protons may be negated to some extent by the production of stray neutrons.

This is of particular concern for paediatric patients!

Existing uncertainties in secondary cancer risks due to neutron production in PT:

- Uncertainties on low-dose cancer risks: linear non-threshold hypothesis?
- Controversy in published risk estimations
- Limited epidemiological data
- Dosimetric challenges
- Large uncertainty on neutron RBE and weighting factor
Introduction: Impact of neutrons in clinical proton therapy

Controversies in published risk estimates:
Radiation protection models are used to convert dose to risk.
1. Neutron dose distribution = additional dose burden to the patient (independently of the delivered dose to the tumour)
2. Neutron dose + therapy protons dose distribution = integral dose to the patient
Published comparisons of neutron dose measurements and the corresponding estimates of cancer risk between different treatment modalities differ over orders of magnitude

Hall: secondary cancer risks is up to 20 times higher for passive PT compared to conventional X-ray therapy (Int J Rad Biol Phys 2006)

Schneider: Decreased secondary cancer risk for active PT and similar risks for passive PT compared to X-ray therapy (Strahlenther Onkol 2006)
Introduction: Impact of neutrons in clinical proton therapy

Controversies in published risk estimates:

schneider – front oncol 2015

Limited epidemiological data:

Data on long-term secondary toxicity and cancer risks in proton therapy is scarce.

One of the first epidemiological studies: a reduction in second cancer risks for active and passive PT compared to X-rays.

Incidence of second malignancies among patients treated with proton versus photon radiation.

Chung DS¹, Yock T, Nelson K, Xu Y, Keating NL, Tarbell NJ

Comparison of cancer risks between different treatment modalities should not be oversimplified. The full dose distribution should be taken into account, particularly the integral dose advantage of PT.
Introduction: Impact of neutrons in clinical proton therapy

Large uncertainty on the neutron RBE and radiation weighting factors

Neutron RBE depends on:

• Energy
• Dose (and dose rate)
• Biological Endpoint
• Influence of fractionation

Limited data available on neutron RBE for relevant endpoints (carcinogenesis)

Very limited data is available on high-energy neutrons (20-250 MeV)
Radiation weighting factor $w_R$ (ICRP) used for cancer risk estimations. Introduced for radiation protection purposes in order to account for the relative detriment of different types of radiation.

- Pooling the RBE data from different experiments
- Conversion of absorbed dose (Gy) to equivalent dose $H$ (Sv)

$$H = w_R \times D$$

- Depends on energy for neutrons: maximum of 20 around 1 MeV. However, most of the dose deposited indirectly via neutrons in PT is deposited by high energy neutrons.
- Recent data obtained with human lymphocytes and 60 MeV quasi-monoenergetic neutrons indicate a mean quality factor that decreases with increasing neutron energy to values of <5: continuous functions used by ICRP

\[
\begin{align*}
    w_R &= \begin{cases} 
    2.5 + 18.2 \sqrt{E_n} / \text{MeV} & \text{for } E_n < 1 \text{ MeV} \\
    5.0 + 17.0 \sqrt{E_n} / \text{MeV} & \text{for } 1 \text{ MeV} \leq E_n < 50 \text{ MeV} \\
    2.5 + 3.25 \sqrt{E_n} / \text{MeV} & \text{for } E_n \geq 50 \text{ MeV}
    \end{cases}
\end{align*}
\]

Introduction: Impact of neutrons in clinical proton therapy

Strong need for radiobiological input to determine $w_R$ for secondary neutrons produced in PT.

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Material & Methods

Since secondary cancer risk are particularly important for children, all positions are located in a 150 mm radius, representing the diameter of the head of a 5-y old child.

Phantom and Irradiation Set-up:

Beam description:
- 200 MeV proton beam (PPT)
- 100 mm R50 range
- 31mm SOBP
- 30mm circular field size

Water tank with Perspex sleeves:
- Lateral positions (85 mm water equivalent depth):
  - A: 25 mm from beam axis – 10 mm from field edge
  - B: 50 mm from beam axis – 35 mm from field edge
  - E: 75 mm from beam axis – 60 mm from field edge

Previous studies have shown that the neutron production and the spectral energy distribution were similar in water compared to an anthropomorphic phantom for PT studies

(Mares et al. – Phys Med Biol 2016)

Material & Methods

It is important to study the deposited energy of all stray components

Separate Perspex sleeves were designed for different detectors:

- Neutron bubble detectors (Bubble Technology Industries)
- Li6 and Li7 enriched thermoluminescent dosimeters (TLDs)
- Silicon-on-insulator microdosimeter (MicroPlus™ Probe)
- T2 ionization chamber for measurement of output factors (Gy/MU)

A ‘pilot’ run of Geant4 Monte Carlo simulations was performed in order to simulate the energy deposition of different stray components in the selected out-of-field positions
Material & Methods

Radiobiological Endpoints:
Whole blood samples from two adult donors were used: the link between chromosomal aberrations in blood cells and cancer in any organ is strengthened by the evidence that chromosomal aberrations are an indicator of genomic instability, which plays a key role in cancer development.

Cytokinesis-Block Micronucleus Assay (CBMN) - Mutagenesis

Dicentric Assays (DIC) and stable aberrations (mFISH) - Exchange-type aberrations have a link with leukaemia, which is important for childhood cancer survivors.

Results

Output Factors:
The output factors indicate that the doses outside the primary field are very low, from 0.6 mGy/Gy for position A down to 0.2 mGy/Gy for position E.

This is in agreement with previous studies illustrating a decrease in absorbed dose outside the primary field with depth.

<table>
<thead>
<tr>
<th>Positions</th>
<th>Output factor (Gy/MU)</th>
<th>STD (%)</th>
<th>Absorbed dose (mGy/Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.00049</td>
<td>1.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Lateral B</td>
<td>0.00026</td>
<td>4.7</td>
<td>0.3</td>
</tr>
<tr>
<td>E</td>
<td>0.00015</td>
<td>10.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Distal C/D</td>
<td>0.00027</td>
<td>2.3</td>
<td>0.3</td>
</tr>
<tr>
<td>SOBP</td>
<td>1.217</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Ent. Plat.</td>
<td>0.899</td>
<td>0.1</td>
<td></td>
</tr>
</tbody>
</table>
Results

Equivalent Dose/Dose equivalent

**Microdosimetry**

**Dose equivalent** by using quality factor Q(L) recommended by ICRP which depends on the lineal energy transfer

**Bubble detectors**

**Equivalent dose** by using the weighting factor ($w_R$) based on the continuous function provided by ICRP.

Are the weighting factors that we use to convert absorbed dose to equivalent dose even appropriate?

Based on this study where we take all stray components into account and determine the RBE of stray radiation out-of-field, the RBE values close to the field edge (<75mm) are not higher than 2...

Discussion and Conclusion

**Limitations and future directions:**

- Investigation of potential angular dependence of solid-state MicroPlus™ probe
- Secondary neutron production depends largely on the facility
- Lymphocytes of children and adults differ in radiosensitivity
- Based on GEANT4 Monte Carlo data, radiobiological investigation of RBE for neutrons with energies relevant to PT will be performed using iThemba LABS’ quasi-mono-energetic neutron beam lines (up to 190 MeV)
- Additional dosimetric and radiobiological investigation of positions close to the field edge (such as position A)
- Passive double-scattering PT beam line at iThemba LABS represents an older generation of PT modalities, there is a need to repeat these measurements and compare our results with more recent active scanning PT systems
Discussion and Conclusion

Conclusions:
• Absorbed doses out-of-field are low, so we have to put radiation risks in perspective
• While there is an exponential decrease in dose, there is an increase in neutron contribution to the total dose as a function from field edge, resulting in higher RBE values
• Although epidemiological evidence indicates that RT makes a crucial contribution to long-term survival of childhood cancer, it is vital that we ensure that any avoidable and detrimental exposures to radiation are as low as reasonably achievable
• Despite large uncertainties, data suggests that particle therapy should lead to a lower risk of secondary cancer compared to conventional X-ray techniques. Modification of treatment units with additional shielding and upgrade to active scanning PT will further reduce the secondary cancer risk in paediatric PT
• Personalised treatment strategies for children, by selecting the radiation type that is likely to have the least detrimental effects

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Thank you for your attention
Any questions???