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Pencil Beam Scanned proton therapy:
Challenges and Opportunities for the 4D treatments

About myself

Born and grew up in Xi'an, China

Xi'an Jiaotong University (China)
B.Sc in Biomedical Engineering

KTH Royal Institute of Technology (Sweden)
M.Sc in Medical Engineering

ETH Zurich & Paul Scherrer Institut (Switzerland)
Ph.D in Medical Physics

Varian Medical Systems
Research Scientist

2014-2016

2010-2013

2008-2010

2004-2008

1986

since 2018/07

Paul Scherrer Institut
Tenure track scientist

Paul Scherrer Institut
Postdoc researcher
The "beauty" of PBS and its current clinical status

Challenges for PBS mobile tumour treatment

Opportunity for Motion mitigation approaches

Opportunity for Image guidance - offline/online

Remaining uncertainties

Outlooks and future research directions

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The principle of radiation therapy

- Energy deposited by radiation (dose = J/kg or Gray) can sterilize cells through the production of free-radicals inside the cell.

- The higher the delivered dose to the whole tumour, the higher the probability of controlling it.

BUT...

- Normal tissues will also be damaged and sterilized by irradiation in a similar way.

The art of radiotherapy then, is to concentrate the dose in the tumour whilst sparing the surrounding normal tissues as much as possible.
Driven force for innovation in RT

- Elekta - Unity
- ViewRay – MRIdian
- Varian TrueBeam
- Cyberknife
- PSI-Gantry2 (PBS proton)
- Heidelberg Ion Therapy Center

<dose is a surrogate for the biological effect>

Main goal of radiation therapy is to Put the dose to where the target is

This means:
- the right = necessary amount of dose
- in optimized = most efficient and best tolerable fractionation
- to the correct location = large enough, but as small and conformal as possible

TCP and NTCP

TCP: Tumour control probability – generally a term used in modelling tumour radiation responses

NTCP: Normal-tissue complication probability – generally a term used in modelling normal-tissue radiation responses

Optimization:
Maximize TCP and minimize NTCP
Physical advantages of proton therapy

- dose conform to target
- dose reduced to OARs
- flexible for dose delivery
- less second neutrons

Proton depth-dose curve
Nuclear Coulomb scattering
Initial beam optics

Beam delivery system for proton therapy

**Cyclotron**
- For therapy application
  - Energy: 75-245 MeV
  - Range: 5-35 cm in water
- Stable and continuous beam
- High beam current
- Intensity modulation
- Single particle (proton)
- Fixed energy

**Synchrotron**
- High energy
- Any particle
- Low radioactivity
- Limited average intensity (ring filling)
- Spill structure – discontinued beam
- Noisy beam intensity

**Passive scattering**
- Delivery dose to the whole target simultaneously

**Active scanning**
- Delivery dose to the whole target sequentially
Lateral spread: *Active* scanning

- Charged particles can be directed by electromagnetic fields.
- Experimental set-up to demonstrate technical feasibility of scanning with protons (PSI, 1990).
- For conformal scanning:
  - Scanner magnets
  - Patient table motion
- Similar developments also at GSI (Germany) and Japan.

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**IMPT - Intensity Modulated Proton Therapy**

Each individual field is highly in-homogenous (in dose) across the target volume (c.f. SFUD plans).
250MeV superconducting cyclotron

Clinical operation since 1996

the first patient treatment on Jul 2018

the first patient treatment on Nov 25th 2013

250->70MeV (~35->4cm in water)

Clinical outcomes

- **Skull base chordomas**
  - 5y Local control: 80%

- **Ependymomas**
  - 5y Local control: 78%

- **Parameningeal Rhadomyosarcomas**
  - 5y Local control: 73%

- **Atypical Teratoid/Rhabdoid**
  - 2y Local control: 66%
Challenges for PBS PT for mobile tumour treatment

Organ motion and 4D treatment

Generally, “motion” can be interpreted as any geometric difference occurring between the phase of planning and the phase of dose delivery:

- Intra-fractional: respiration, heart beating (deformable movement)
- In between: digesting movement, muscle relaxation (deformation, drift)
- Inter-fractional: anatomy variation (grows, shrink, shift)
Uncertainties for *intra*-fractional motion

Characteristics of the motion-induced dosimetric uncertainties

- lateral dose conformity
- dose homogeneity
- distal dose conformity
Challenges in PT – dealing with uncertainties

- Potential magnitude
  - Beam energy \( [\sigma] \)
  - Patient positioning \( [\sigma] \)
  - Inherent CT uncertainties (beam hardening, calibration etc) \( [\Sigma] \)
  - Distal end RBE enhancements \( [\Sigma] \)
  - CT artifacts \( [\Sigma] \)
  - Variations in patient anatomy \( [\Sigma, \sigma] \)

Precise
Sensitive

Interplay effects for 4D PBS proton treatments

- The interplay effect are significant, individualized and can be influenced by many 4D parameters
- 4D dose distribution patterns is very difficult to predict without appropriate modelling the dynamics from both moving organ and PBS-based dose delivery

Effects of PBS scanning dynamics

Effects of motion amplitude

Motion ~5mm
Motion ~15mm
Motion ~20mm
Sensitivity due to 4D input parameters

4D plan is rather sensitive to all input factors from either machine side or patient side. It can be risky to make any conclusion or decision when only certain parameters are considered.

Overview of the 4D parameters

1. Patient geometry
2. Field direction
3. Field arrangement
4. PBS beam data
5. Spot distance
6. Energy layer distance
7. Prescribed dose
8. Fractionation scheme
9. 3D plan – density: Max/mean/midV CT
10. 3D plan – geometry: CTV/gITV/rITV
11. Scanning path/direction

Motion pattern and variation
11. Period
12. Amplitude
13. Irregularity
14. Deformation

Beam delivery dynamics
15. Lateral position: Raster or spot
16. Dose rate: varied or constant
17. Energy switching time
18. Starting phase and combination for multi-fields

Motion mitigation approach
19. Rescan type and number
20. Combined with gating: GWs, surrogate
21. Combined with Tracking
22. 4D optimization

It is really a high dimension problem...
4D dose calculation – the approach for assessing motion effects and uncertainties

4DDC consists of two components:

- time resolved PBS dose calculation
- 4D patient model – quantified by deformable motion fields

It can provide a systematical evaluation for understanding the 4D problems for individual patient under specific 4D scenarios

Portfolio for motion mitigation strategies
Breath-hold: request fast dose delivery

**Technical challenges**
- Max. beam current for Cyclotron
- Energy dependent beamline transmission
- Max. acceptable beam current for beam diagnostic
- Achieve the minimal spot duration

**Plan requirements**
- High spot weight dynamics with each energy layer varies up to 10 times
- More low weight spots due to rescanning
- Capability to irradiate small weight spot

**Example clinical plan**
- Spot below yellow threshold cannot receive max dose rate of its energy layer

**Reducing field delivery time by increasing proton beam current?**

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Then... Handling the problem to interfractional motion -> online plan adaptation

**Planning CT**
**Repeat CT**

**Initial plan**
**Recalculated plan**
**Adaptive plan**

by Lena Nenoff (collaboration PSI and Uni Lund)
Re-gating: a practical approach

- easy to implement
- prolonged treatment duration
- extended irradiation volume
- appropriate ITV predefined
- scanning dynamic dependent
- need sufficient rescan number
- Statistical averaging is insufficient for large motion

- not difficult to implement
- prolonged treatment duration
- Restricted target volume expansion
- need to tackle the residual motion (with rescanning)
- need online motion monitoring and correlation
- need to update gating window (baseline shift)

A comprehensive evaluation of re-gating

Zhang et al 2018 Radiotherapy & Oncology
4D optimization: making 4D plan motion robust by itself

**Advantage**
- No prolonged delivery time
- No extended ITV margin

**Disadvantage**
- Sensitive to difference in motion for optimization and for delivery (if motion used by 4D optimization was not reproducible for validation, optimized dose homogeneity would collapsed)

Graeff et al 2014 PMB
Bernatowicz et al Jan 2017 PMB
Zhang et al ESTRO2018, AAPM2018
Engwall et al AAP 2018

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How to obtain accurate and reliable motion?

**Synthetic 4DCT-MRI**
- Single patient geometry modulated by different deformable motions
- Different patient geometries modulated by the “same” motion
- Single patient geometry modulated by regular or irregular motion patterns

4D patient is “less reproducible” than a PBS proton machine. The caught motion is only a snapshot …

=> online image guidance is important for QA
The synthetic 4DCT-MR approach

4DMRI (PSI) → Motion vectors

Single phase from 4DCT (KSA) → Volumetric image deformation

4DCT(MRI) (KSA + PSI)

4D-MRI of patient

Register static CT to MR reference phase

Warp static CT

Apply bodymask on VF

Extract VF to reference phase (end exhale)

resample VF to CT spacing

5 4DCT(MRI) for this patient

K. Dolde et al 2018 PMB
The usually neglected motion variability

36 Breathing cycles for 1st KSA patient extracted from 4DMRI acquired at PSI

4DCT(MRI) Cycle 1 (KSA+PSI)
4DCT(MRI) Cycle 5 (KSA+PSI)
4DCT(MRI) Cycle 7 (KSA+PSI)
4DCT(MRI) Cycle 13 (KSA+PSI)

Original 4DCT (KSA)

Single phase of lung cancer 4D CT from open source database

4D MRI in lung of volunteer

ITV volumes calculated from different cycles
Beam tracking: following tumour as its current situation

- Real-time motion monitoring without “too much additional” imaging dose
- Low latency (~50ms) measurements with high accuracy (<1mm)
- Fast energy adaptation with good beam quality
- Capable to adapt treatment field according to real-time updates

Importance to have online image guidance

**Why IGPT is needed?**
- Scanned proton is sensitive to small motion and density variation
- Respiratory motion is varied and irregular

**How to use IGPT?**
- Know where is the dose delivered to (4D dose reconstruction)
- Online motion compensation (image guided beam gating or tracking)
Geometry calibration of on-board BEV imaging system

- To derive geometry parameter in reality
- To calculate exact DRR images
- To derive the magnification factor

On-line 2D motion tracking using the BEV imaging system

- Imaging frequency: 3 Hz
- Breathing cycle: 6 s
- Fiducial marker: Visicoil Gold
  - Length: 5 cm
  - Diameter: 1.1 mm
- Detection error < 0.5 mm
- Detection efficiency > 95%

BEV imaging system is capable to online track the internal 2D motion from the same direction of therapeutic beam (maximally resolve lateral motion)
On-line surrogate motion tracking (BEV-DRRs)

Bridging the gap of online and offline information

Capture example motion
- 4DMRI + DIR
- Obtaining correlation using PCA

Pre-treatment

online deformable motion prediction

patient specific motion model

4DCT reconstruction

online traced sparse surrogate motion

Conventional motion tracking

Deformable motion tracking

Zhang et al 2013 PMB
Online deformable motion reconstruction – spatial accuracy

Enable the possibility of online deriving:
- spatial motion differences
- lost motion component in imaging direction
- density variation
- Tackle the trade-off between real time and volumetric imaging

Retrospective 4D dose reconstruction

Accuracy of estimated motions:
≈ similarity of their 4DDC
- 4D plans considering either ground truth motions or predicted motions
- absolute dose difference
- Dose Different Volume Histograms (DDVH) in Irradiation Volume (IV)
- $V_{\text{dosediff}} = 5\%$

Online image guided beam tracking

- Beam (Bragg peak) specific lateral motion compensation vectors derived from online prediction deformable motion fields
- Beam specific range compensation value derived from the reconstructed CT

Beam tracking only cannot fully restore the dose homogeneity of the static plan, due to extensive organ rotation and deformation

Model-based IGPT to lung scenarios...

- Liver 2D US
- Lung 4DMRI

Building motion model

PBS Tracking

Ideal tracking
Realistic tracking

Ongoing SNF Grant No. 320030_163330/1
Krieger and Giger et al, oral presentation ICCR2019
Uncertainties – experimental validation for 4DDC

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<tr>
<td>Mean</td>
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</tbody>
</table>

Krieger et al PMB 2018

Uncertainties – deformable registration

4DCT/MRI dataset

Ground truth plan

4DCT/MRI dataset

Estimated 4D plans using 6 different DIR methods

DIR1

DIR2

DIR3

DIR4

DIR5

DIR6

DVH (CTV)

Ribeiro et al RO 2018 (PSI and UMCG)
Uncertainties – temporal resolution for 4DDC

(a) Spot wise  (b) 4D image wise  (c) Absolute difference

(d) \( V_{dose_{diff}} > 5\% \)

Zhang et al PMB 2019

Outlooks

Machine learning in PT?  Online MR guided PT?


Knowledge is powerful  Personalization is critical
**FLASH**

HYPL-PT induces a transient radiation-induced hypoxia that protects only the normoxic tissues.

Vozenin et al. Clin Cancer Res 2018

**Grid/micro beam therapy**

**Summary for PBS 4D treatments**

- **4DDC** is an important risk analysis tool for patient specific motion mitigation selection.
- Motion is a problem, but could be partially dealt with using simple (gating, breath-hold, re-scanning) or more challenging techniques (tracking, re-tracking, 4D optimization).
- **Online image guidance** is important for treatment QA, and **Motion model** is useful for combining online and offline information.
- **Beam tracking** and **4D optimization** will ameliorate 4D PBS treatments in future.
- There are many upcoming opportunities/trends for improving the current solutions.
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