PET-based treatment verification: status and perspectives

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The quest for precision

The finite range with the characteristic “Bragg-peak”

... increased sensitivity to uncertainties

Range uncertainties

Tx planning uncertainties
- CT-range calibration
- Imaging artefacts
- Calculation models

Delivery uncertainties
- Inter- and intra-fractional anatomical changes
The quest for imaging

Obtain knowledge of:
- patient position and anatomy
- Inter- and intra-fractional motion
- In-vivo range
- (deposited dose)

Imaging of secondary radiation from nuclear reactions
Transmission imaging (e.g., WE-D-BRF-4)

In-vivo PET-based verification

\[ A(r) \neq D(r) \]

Tradeoff between better spatial correlation (\( ^{12}\text{C} \)) and stronger signal (\( p \))
Dose-guidance from comparison of measured vs expected \( \beta^+ \)-activity

The possible workflows

PET is a dynamic process, depending on time of irradiation and acquisition
Clinical implementation of in-beam PET

In-beam PET
- Patient in treatment position
- Detection of short lived emitters ($^{15}$O)
- No prolongation of treatment session
- Morphological information from planning CT
  - Limited-angle detection
  - High integration costs

Installation at GSI Darmstadt used clinically for scanned $^{14}$C ions

Enghardt, … Parodi … Nucl Instrum Meth A 2004; Parodi et al Nucl Instrum Meth A 2005

Clinical workflow of ibPET@GSI

Once

> 400 patients

Verification of
- Beam range
- Lateral position

In case of deviation
- Timely reaction

Enghardt, … Parodi … Nucl Instrum Meth A 2004; Parodi et al Nucl Instrum Meth A 2005

Clinical results of ibPET@GSI

In-vivo validation of CT-range calibration curve

Prediction

1998

Experimental refinement of R(HU) calibration in tissue samples

Measurement

Eliminate or reduce systematic error

Clinical results of ibPET@GSI

In-vivo indicator of deviations in actual dose application

Parodi Ph.D. Thesis TU Dresden 2004; Enghardt, Parodi... Radiother Oncol 2004

Clinical results of ibPET@GSI

Indirect estimation of 12C dose deviation from in-beam PET

Dose recalculation

Hypothesis on the reason for the deviation from the treatment plan

Interactive CT manipulation

CT after PET findings

Parodi Ph.D. Thesis TU Dresden 2004; Enghardt, Parodi... Radiother Oncol 2004

Clinical implementation of offline PET/CT

Offline PET/CT
- Full ring scanner
- Comparably low cost
- CT-image for co-registration (extra dose)
- Patient re-positioning (if not using shuttle)
- ~ 5–20 min time delay from irradiation to imaging (washout, counting statistics)
- Long scan time (~ 20–30 min)

Parodi et al, IJRBP 2007; Parodi et al, IEEE CR 2011; Bauer,... Parodi, Radiother Oncol 2013
Clinical experience of offline PET/CT $^{12}$C @HIT

- Enhanced distal activity edge due to $^{12}$C projectile fragments
- Reliable extraction of range information despite washout (brain) and motion (liver, mitigated by belly compressor)

Clinical experience of offline PET/CT $^{12}$C @HIT

- Suspected mispositioning supported by new simulation on CT from PET/CT
- New treatment plan was performed to improve robustness against variations

Range difference map in BEV

$^{12}$C $\sim$ 17 min
$\sim$ 13 min
30 min

Clinical experience of offline PET/CT $^p$ @ MGH/HIT

Reliable range in bony structures
Challenges from knowledge of biological washout and elemental tissue composition

Shen, …, to be published
Clinical implementation of in-room PET

In-room PET
- Patient in treatment position
- Full ring scanner possible
- Few minutes acquisition sufficient
- Patient throughput
- Co-registration uncertainties if moving table

Clinical results of in-room PET@NCC

Experience from dual-head in-room PET at NCC Kashiwa (p)
- 200 s acquisition after end of irradiation found sufficient for imaging
- Detection of inter-fractional delivery / anatomy changes

Clinical results of in-room PET@NCC

Replanning triggered by PET finding

\[ R_{max} (plan(b) - plan(a)) \]
- \(-21.1\) mmWEL: port1
- \(-15.0\) mmWEL: port2
- \(-17.2\) mmWEL: port3

Nishio et al, IJROBP 2010; Courtesy of T. Nishio, NCC Kashiwa
Experience from dual-head in-room PET at NCC Kashiwa (p)
- 200 s acquisition after end of irradiation found sufficient for imaging
- Detection of inter-fractional delivery / anatomy changes

Assessment of reproducibility (daily activity compared to reference meas.)
- Small planar system optimised for animal imaging, limited FOV
- No acquisition possible during beam-on time

Nishio et al, IJROBP 2010; Courtesy of T. Nishio, NCC Kashiwa

Experience from full-ring in-room PET at MGH (p)
- 5 min measurement started 2 min after irradiation end
- Range agreement mostly within ±3 mm (4 - 11 mm rms)
- ~ 2 mm co-registration errors despite robotic couch and radioactive markers
- Limited bore of scanner (only head and pediatric cases)

Zhou et al PMB 2011, Min et al IJROBP 2013

Clinical results of in-room PET@NCC

Clinical results of in-room PET@MGH

R&D challenges

All the reported experiences suggest feasibility and potential value

Remaining limitations of PET-based verification
- Inaccurate prediction of activity distributions due to insufficient knowledge of nuclear reaction cross sections and tissue composition
- Degradation of activity distributions by washout and organ motion
- Time-consuming evaluation requiring well trained staff
- Imaging performances and integration costs for on-site implementations

Ongoing efforts to ...
Modeling of proton PET prediction

- Improve MC prediction via experimental based adjustment of $\beta^+$ cross sections
- Speed up calculation with analytical models using same TPS pencil beam algorithms
- Overcome limitations of CT-based tissue classification via MRI or DECT

Modeling of activity washout

- Improve washout modeling on the basis of animal studies

4D PET-based verification

- Phantom and clinical studies on detectability of range changes and interplay effects in the presence of motion

*Courtesy G. El Fakhri, PhD*
Automated range assessment

- Robust automated range assessment from PET distributions (meas. vs calc., meas. vs meas.), % fall-off, shift analysis, volumetric analysis

Hardware improvements: dual head solutions

- Detector developments towards ultra-fast Time-of-Flight (TOF) in-beam PET

Hardware improvements: full ring solutions

- Prototype small bore PET/CT scanner just started clinical study at MGH
- Large scale in-beam full ring openPET scanner prototype being developed and tested with stable and radioactive ion beams at NIRS
Hardware improvements: towards hybrid detectors?

- Hybrid detector systems to detect
  - prompt γ rays during irradiation
  - delayed γ rays (from β⁺ emitters) during irradiation

Conclusions and outlook

- Clinical investigations of PET monitoring being reported for different centers with different ions and delivery systems, as well as different scanners (mostly adapted from nuclear medicine or small animal imaging)

- Despite promising results (+3mm range verification accuracy in favorable H&N locations), several issues remain (counting statistics, washout, co-registration and motion in extra-cranial sites, …)

- Several groups are pursuing methodological improvements, but major advancement being expected by next generation in-beam PET scanners specifically optimized for this application

- Although many promising new techniques are on the horizon, PET could still play a role due to its intrinsic 3D, molecular imaging capabilities when properly used to detect the major ¹⁵O contribution in the tumour

⇒ hybrid imaging approaches e.g., combining PET with prompt γ?

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Accuracy of in-beam PET range verification?

"In-silico" trial on patient treated at GSI (Head&Neck)

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<tr>
<th>Planned dose</th>
<th>Reference PET</th>
<th>PET for increased range</th>
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<tbody>
<tr>
<td>Overrange detection</td>
<td>Specificity 96 ± 2 %</td>
<td>Specificity 95 ± 2 %</td>
</tr>
<tr>
<td>Underrange detection</td>
<td>Sensitivity 91 ± 3 %</td>
<td>Sensitivity 92 ± 3 %</td>
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Fiedler et al PMB 2010

Outlook: image quality

- Offline PET imaging suffers from several limitations
- Optimizing imaging parameters can yield significant improvements

Ph.D. Thesis C. Kurz; Kurz, ...,. Conti, Parodi, presented at IEEE MIC 2013 Seoul

Novel PET systems for in-room imaging

Dual-head scanner mounted on rotating gantry in Kashiwa, Japan

- Distance between two opposing detector heads of 30 - 100 cm
- Isocentric rotating of 0 - 360 deg.
- Position resolution of 1.6 - 2.1 mm FWHM
- Detection area of 164.8 × 167.0 mm²

- Planar imaging starting immediately after end of irradiation (cyclotron)
- A/r ≠ D/r: Daily measurement compared to reference activity (reproducibility check)
- > 50 patients of H&N, Liver, Lung, Prostate and Brain from 2007/10

Similar finding as for GSI (e.g., detection of anatomical changes)

- Courtesy of T. Nishio NCC-Kashiwa, Nishio et al IJROBP 2010