PET-based treatment verification: status and perspectives

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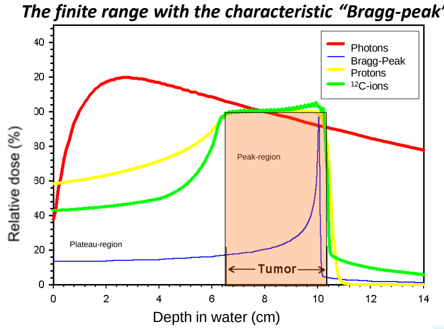
The quest for precision

The finite range with the characteristic "Bragg-peak"

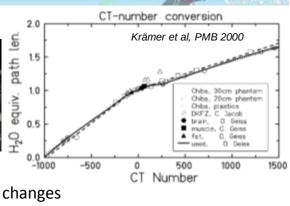


… increased sensitivity to uncertainties

Range uncertainties

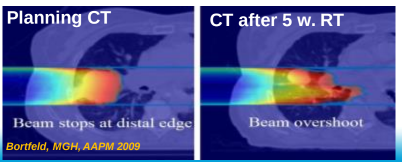
Tx planning uncertainties

- CT-range calibration
- Imaging artefacts
- Calculation models



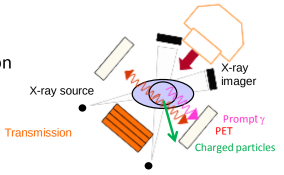
Delivery uncertainties

- Inter- and intra-fractional anatomical changes



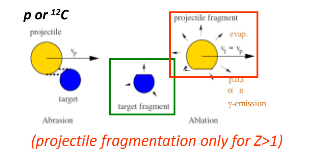
The quest for imaging

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



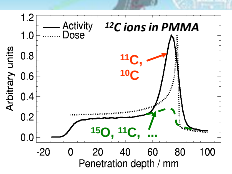
(projectile fragmentation only for Z>1)

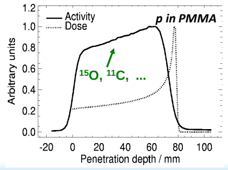
β^+-emitter yield (^{15}O, ^{11}C,..., with $T_{1/2}$ ~ 2, 20,... min) as by-product of irradiation

A(r) ≠ D(r)

Tradeoff between **better spatial correlation** (^{12}C) and **stronger signal** (*p*)

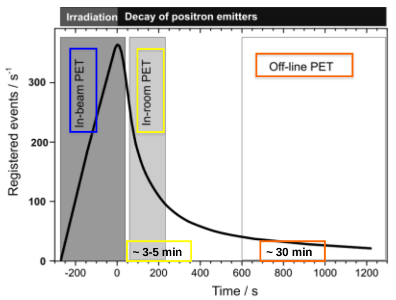
Dose-guidance from comparison of **measured** vs **expected** β^+-activity





K. Parodi et al, IEEE TNS 2005

The possible workflows



PET is a dynamic process, depending on time of irradiation and acquisition

Shakirin, ..., Parodi, ... PMB 2011

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
- o Morphological information from planning CT
- \- Limited-angle detection
- \- High integration costs

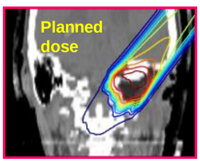
Installation at GSI Darmstadt used clinically for scanned ^{12}C ions

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

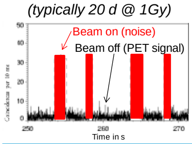
Clinical workflow of ibPET@GSI

Once

> 400 patients



For every fraction (typically 20 d @ 1Gy)

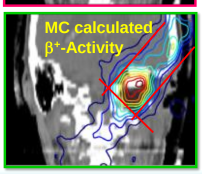


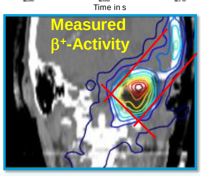
Verification of

- Beam range
- Lateral position

In case of deviation

- Timely reaction

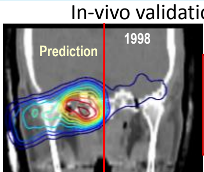




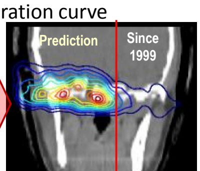
Enghardt, … Parodi … Nucl Instrum Meth A 2004; Parodi et al Nucl Instrum Meth A 2005

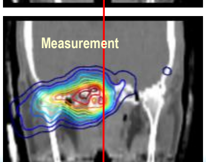
Clinical results of ibPET@GSI

In-vivo validation of CT-range calibration curve

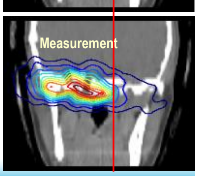


Experimental refinement of R(HU) calibration in tissue samples





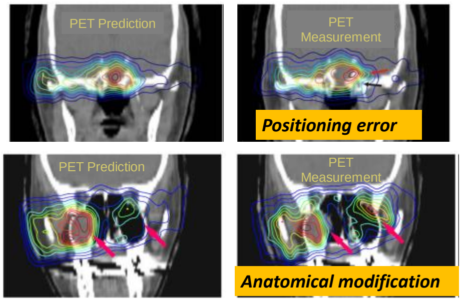
Eliminate or reduce systematic error



Enghardt, et al GSI Report 2004; Schardt et al, GSI report 2007; Rietzel et al, Rad Oncol 2007

Clinical results of ibPET@GSI

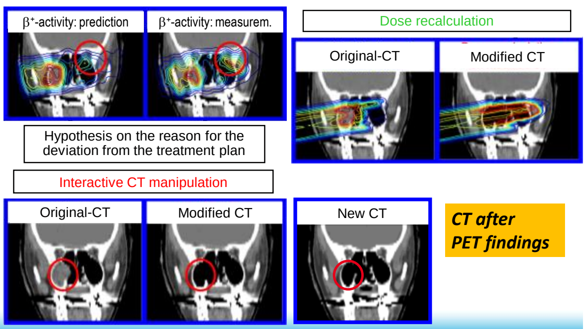
In-vivo indicator of deviations in actual dose application



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

Clinical results of ibPET@GSI

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

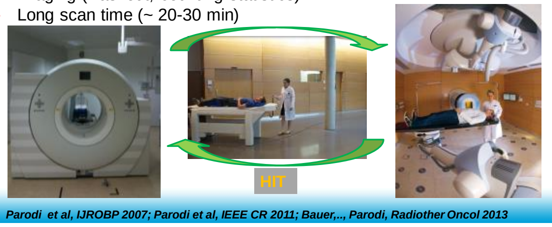


Parodi Ph.D. Thesis TU Dresden 2004; Enghardt, Parodi … Radiother Oncol 2004

Clinical implementation of offline PET/CT

Offline PET/CT

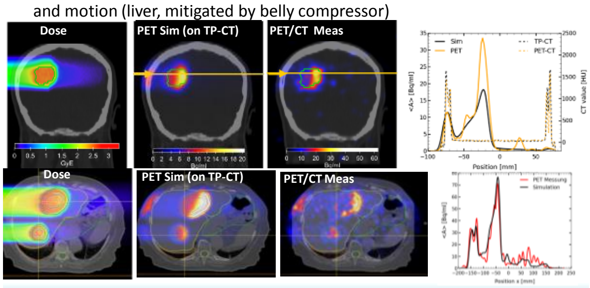
- \+ Full ring scanner
- \+ Comparably low cost
- ○ CT-image for co-registration (extra dose)
- \- Patient re-positioning (if not using shuttle)
- \- ~ 5–20 min time delay from irradiation to imaging (washout, counting statistics)
- \- Long scan time (~ 20-30 min)



Parodi et al, IJROBP 2007; Parodi et al, IEEE CR 2011; Bauer,.., Parodi, Radiother Oncol 2013

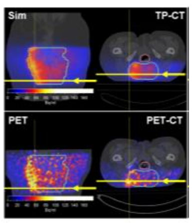
Clinical experience of offline PET/CT ^{12}C @HIT

- Enhanced distal activity edge due to ^{11}C projectile fragments
- Reliable extraction of range information despite washout (brain) and motion (liver, mitigated by belly compressor)

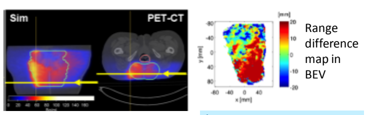


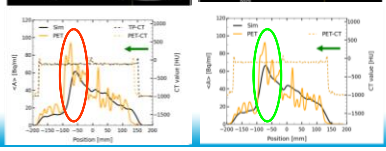
Bauer, …, Parodi, Radiother Oncol 2013

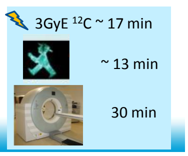
Clinical experience of offline PET/CT ^{12}C @HIT



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

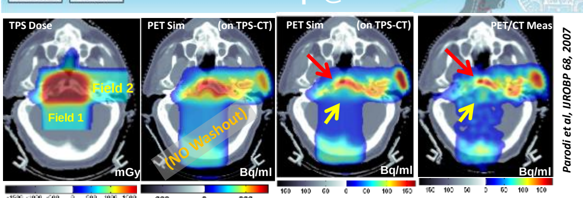




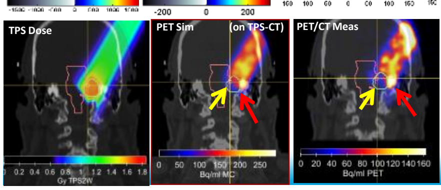


Bauer, …, Parodi, Radiother Oncol 2013

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



Parodi et al, IJROBP 68, 2007



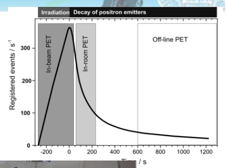
Reliable range in **bony structures**

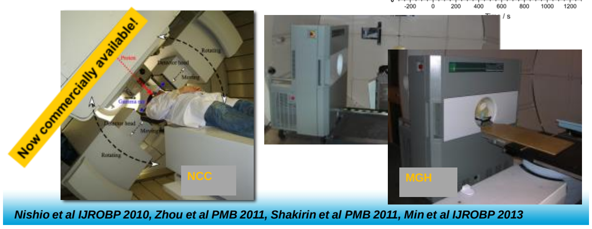
Challenges from knowledge of **biological washout** and **elemental tissue composition**

Bauer, …, 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

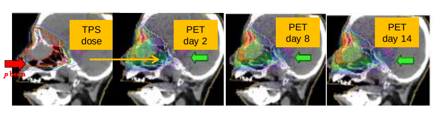




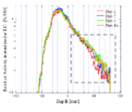
Nishio et al IJROBP 2010, Zhou et al PMB 2011, Shakirin et al PMB 2011, Min et al IJROBP 2013

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



Scattered protons

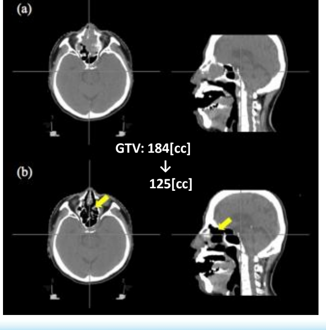


Nishio et al, IJROBP 2010; Courtesy of T. Nishio, NCC Kashiwa

Clinical results of in-room PET@NCC

Replanning triggered by PET finding

$$\Delta R_{max}(\text{plan(b)} - \text{plan(a)}) = \begin{cases} -21.1\ \text{mmWEl: port1} \\ -15.0\ \text{mmWEL: port2} \\ -17.2\ \text{mmWEL: port3} \end{cases}$$



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

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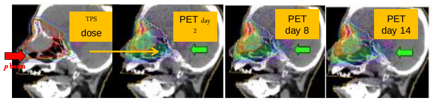
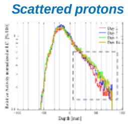




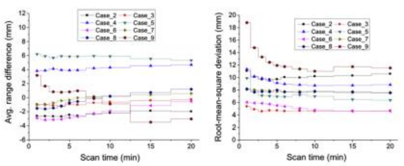
- ○ Assessment of reproducibility (daily activity compared to reference meas.)
- \- Small planar system optimised for animal imaging, limited FOV
- \- No acquisition possible during beam-on time

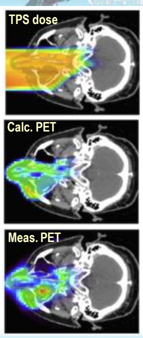
Nishio et al, IJROBP 2010; Courtesy of T. Nishio, NCC Kashiwa

Clinical results of in-room PET@MGH

Experience from full-ring in-room PET at MGH (p)

+ 5 min measurement started 2 min after irradiation end similar to 20 min scan
+ 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

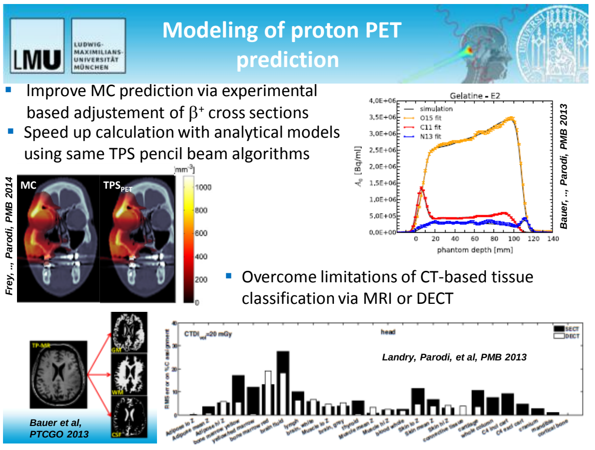
R&D challenges

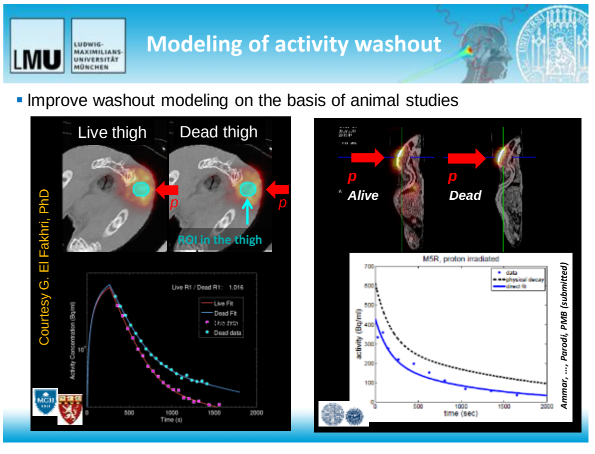
All the reported experiences suggest feasibility and potential value

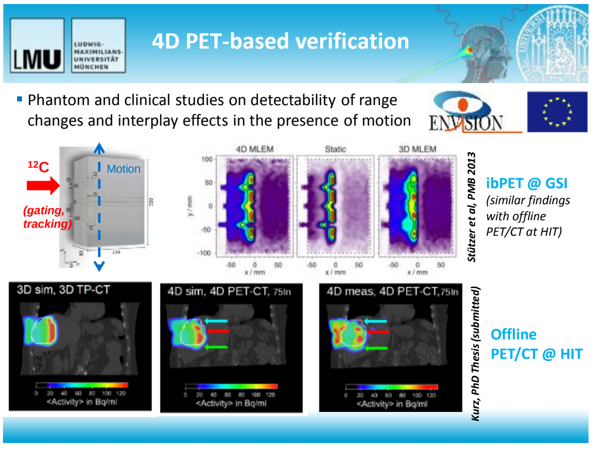
Remaining limitations of PET-based verification

- 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 adjustement of β+ cross sections
Speed up calculation with analytical models using same TPS pencil beam algorithms
Frey, .., Parodi, PMB 2014
MC
TPS
Gelatine - E2
simulation
O15 fit
C11 fit
N13 fit
phantom depth [mm]
Bauer, .., Parodi, PMB 2013
Overcome limitations of CT-based tissue classification via MRI or DECT
Landry, Parodi, et al, PMB 2013
Bauer et al, PTCGO 2013

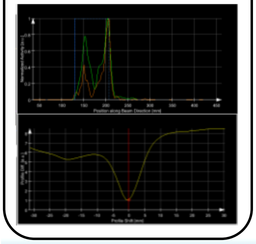

Modeling of activity washout
Improve washout modeling on the basis of animal studies
Live thigh
Dead thigh
ROI in the thigh
Courtesy G. El Fakhri, PhD
Alive
Dead
M5R, proton irradiated
time (sec)
Ammar, ..., Parodi, PMB (submitted)


4D PET-based verification
Phantom and clinical studies on detectability of range changes and interplay effects in the presence of motion
ENVISION
12C
Motion
(gating, tracking)
4D MLEM
Static
3D MLEM
Stützer et al, PMB 2013
ibPET @ GSI
(similar findings with offline PET/CT at HIT)
3D sim, 3D TP-CT
4D sim, 4D PET-CT
4D meas, 4D PET-CT
<Activity> in Bq/ml
Kurz, PhD Thesis (submitted)
Offline PET/CT @ HIT

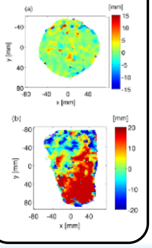
Automated range assessment

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

Automated shift analysis



BEV range difference



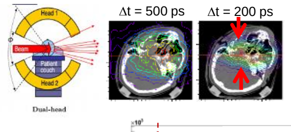
Intervention?

Decision support system for clinical workflow

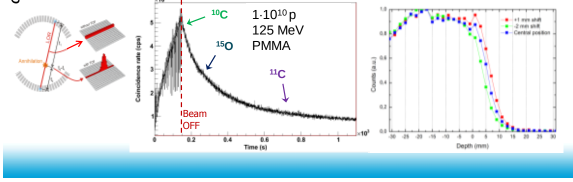
Unholtz, …, Parodi, IEEE MIC Conf. Rec. 2011; Helmbrecht et al, PMB 2012; Frey, …, Parodi, PMB (submitted)

Hardware improvements: dual head solutions

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



Crespo et al, PMB 2007



P. Cambraia Lopes et al, presented at IEEE MIC 2013

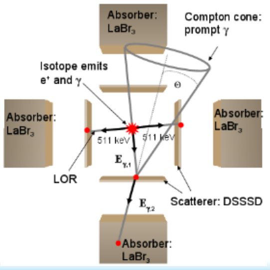
Hardware improvements: full ring solutions

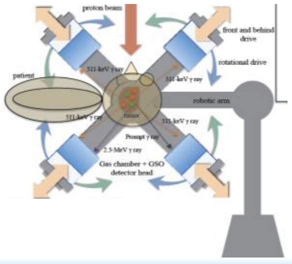
- Prototype small bore PET/CT scanner just started clinical study at MGH
- Large scale in-beam full ring openPET scanner prototype being developed and tested with stable and radioactive ion beams at NIRS

Courtesy G. El Fakhri, PhD

Hardware improvements: towards hybrid detectors?

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





Lang, ..., Parodi, Thirolf, JINST 2014

Courtesy T. Nishio, A. Miyatake, NCC Kashiwa

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 ^{15}O contribution in the tumour**

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

Acknowledgements

The MC-modeling and in-vivo imaging research group at HIT / UKL-HD

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Colleagues at HIT / UKL-HD

J. Debus, S.E. Combs (now TUM) and team

New team at LMU

Collaborators & contributors

G. Baroni et al, Polimi
D.R.Schaart et al, TUD
W. Enghardt et al, Oncoray
T. Bortfeld et al, MGH
T. Nishio et al, NHCC
T. Yamaya et al, NIRS
G. El Fakhri et al, MGH

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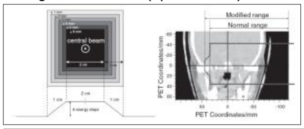
FP7 ENVISION
BMBF SPARTA
DFG (MAP, HICT, KFO)

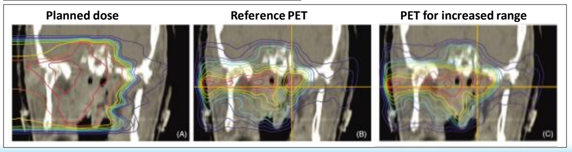
Accuracy of in-beam PET range verification?

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

Range modification (up to ± 6mm) and visual evaluation by experienced person



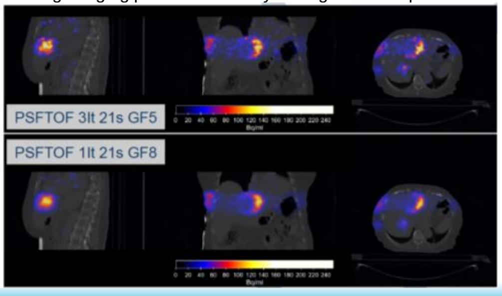
	Overrange detection	*Underrange detection*
Specificity	96 ± 2 %	96 ± 2 %
Sensitivity	91 ± 3 %	92 ± 3 %



Fiedler et al PMB 2010

Outlook: image quality

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

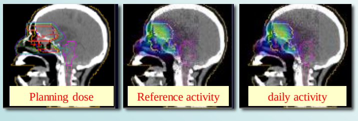


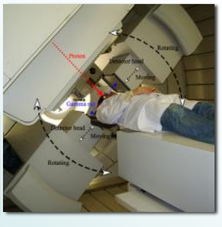
Ph.D. Thesis C. Kurz; Kurz, ...,, Conti, Parodi, presented at IEEE MIC 2013 Seoul

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
- Icentric rotating of 0 -360 deg.
- Position resolution of 1.6-2.1 mm FWHM
- Detection area of 164.8 × 167.0 mm^2





- 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