Technologies Addressing the Range Uncertainty of Ion Therapy: Positron-Emission-Tomography

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Outline

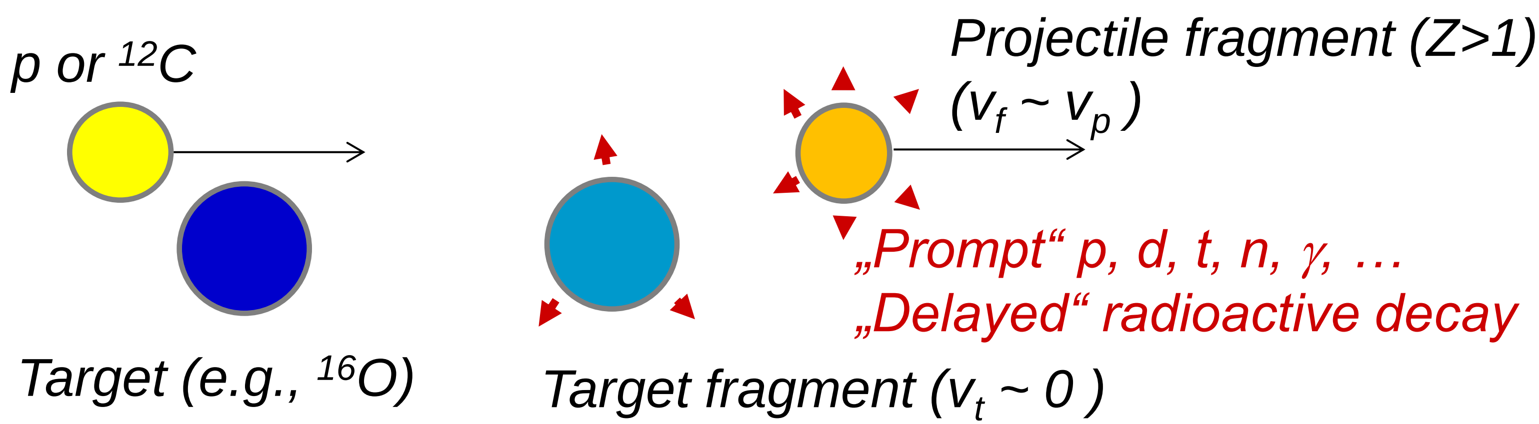
PET-based verification

- Basic principle
- Clinical implementation and experience
- R&D challenges (and opportunities)
- Conclusion and outlook

In-vivo visualization of treatment

- Primary ions are stopped *somewhere* within the patient, with dose and range mainly dependent on Coulomb interaction

- Nuclear reactions induce measurable emerging radiation

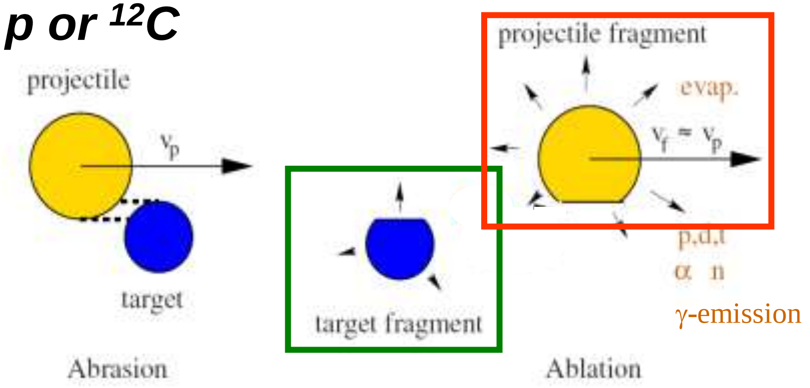


- Secondary radiation can be used as surrogate signal to infer information on the beam range and treatment delivery

Only Positron-Emission-Tomography clinically investigated so far

In-vivo PET-based verification

***p* or ^{12}C**



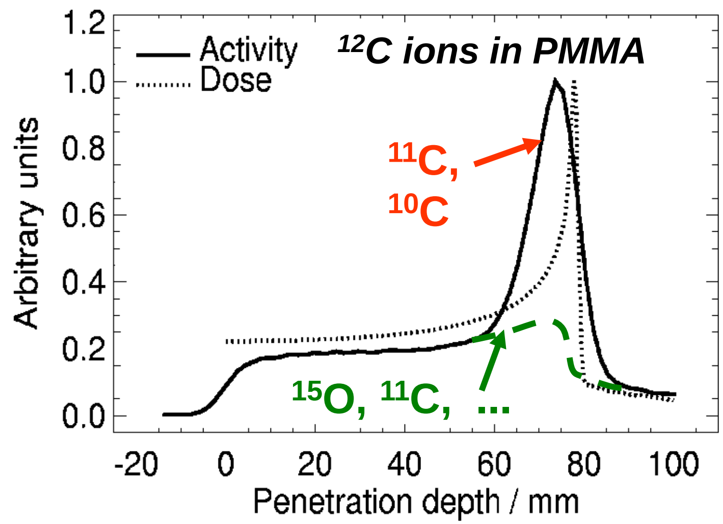
(projectile fragmentation only for Z>1)

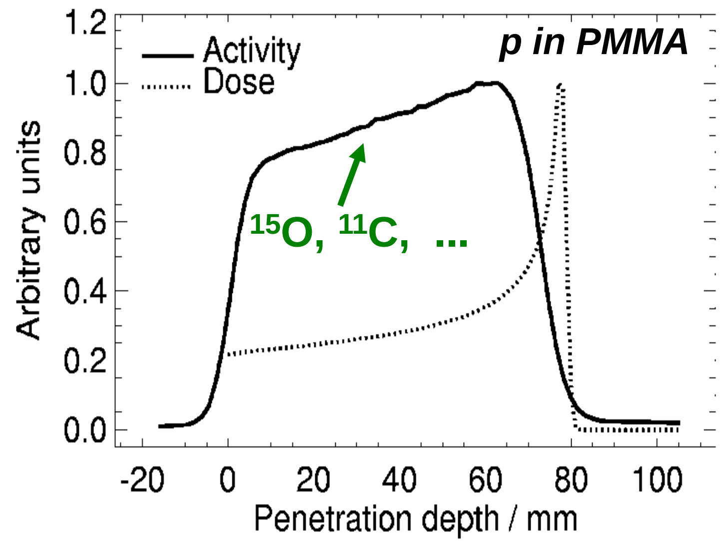
β^+-emitter yield (^{15}O, ^{11}C,..., with $T_{1/2}$ ~ 2, 20,... min) as by-product of irradiation

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

Clinical implementation (I): ibPET

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
- \- Suitable for pulsed beam delivery (measurement only in beam-off times)

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

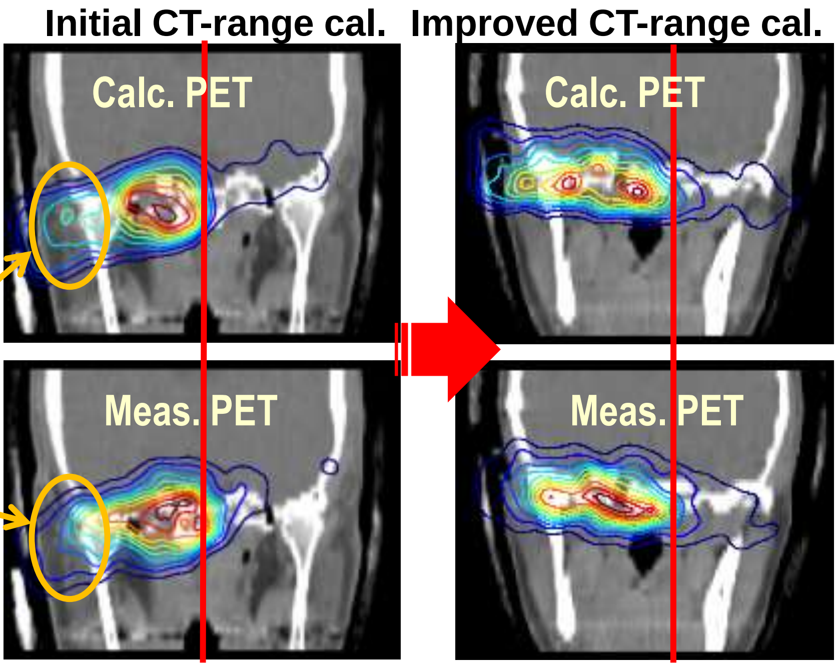
Clinical implementation (I): ibPET

Experience from ibPET at GSI

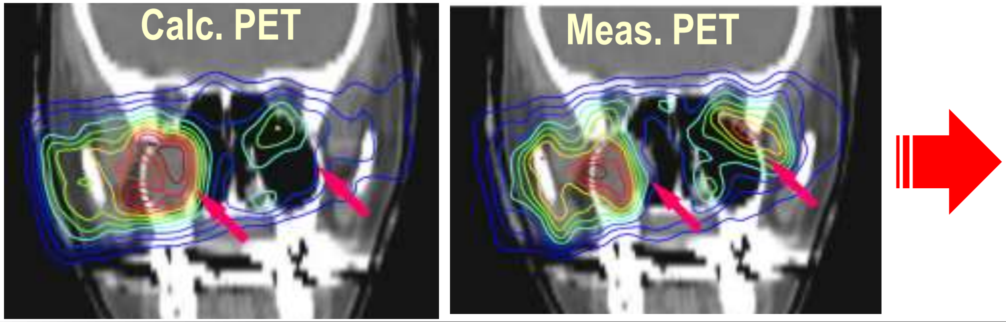
+ Validation of TPS CT-range calibration
+ Detection of mispositioning and anatomy changes with indirect dose quantification
+ > 90% sensitivity / specificity in detecting ±6 mm range changes *(in-silico trial)*

○ Minor degradation from washout

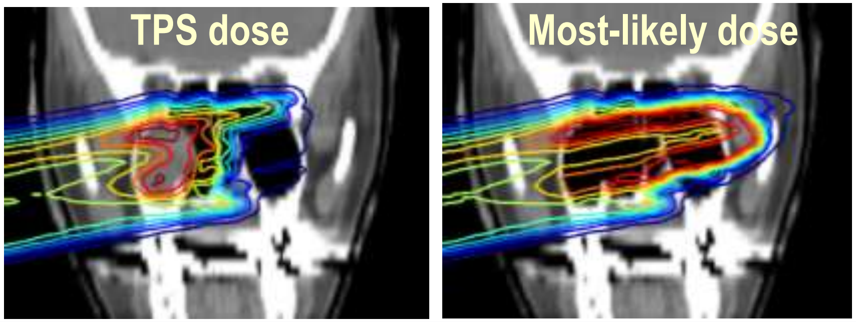
- Non-quantitative imaging, severe limited-angle artifacts in extra-cranial sites
- Low counting statistics



Detection of over-range due to anatomy chage



PET-based dose quantification

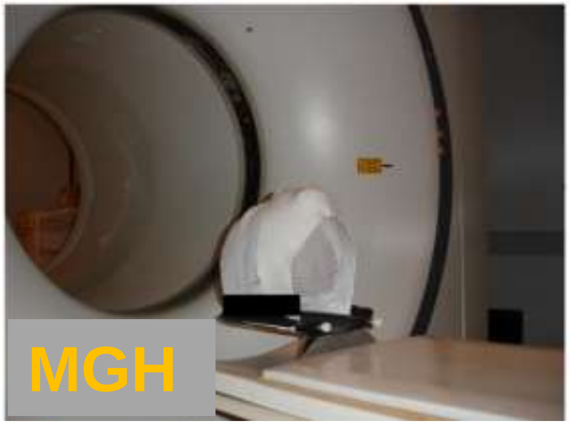


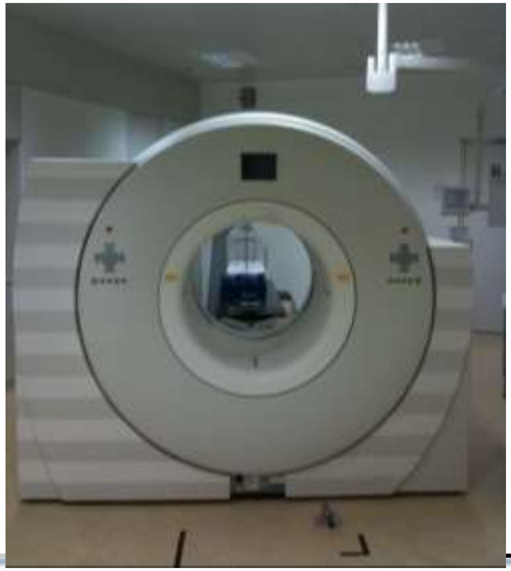
Enghardt, … Parodi … Nucl Instrum Meth A 2004; Parodi PhD Thesis 2004; Fiedler et al, PMB 2010

Clinical implementation (II): offline

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)





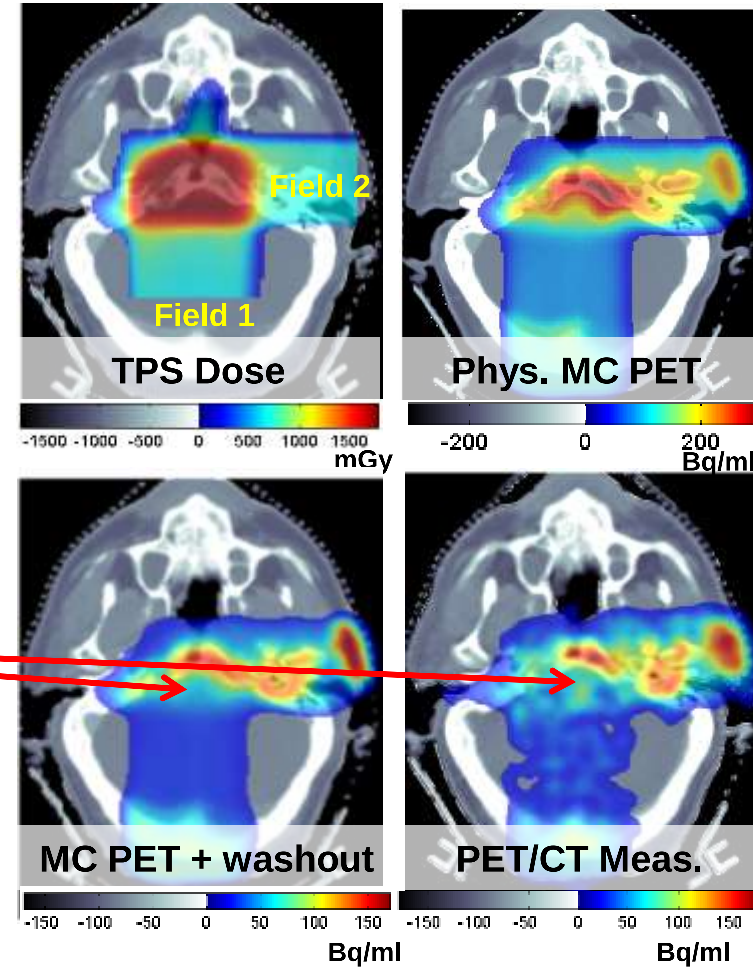
Parodi et al, IJROBP 2007; Parodi et al, IEEE CR 2011; Bauer,.., Parodi, Radiother Oncol 2013

Clinical implementation (II): offline PET/CT

Experience from offline PET/CT at MGH (p)

+ Activation detected in all subjects
+ Washout modeling included in PET prediction
+ Feasibility of ± 3mm range monitoring in well co-registered and low perfused tissues (H&N)
- Low counting statistics
- Improper tissue classification from CT alone
- Limitations of universal washout modeling
- Co-registration and motion blurring in extra-cranial sites

Scattered protons



Tumor location	Biologic washout	Motion	MC uncertainties	Beam direction	CT fusion	Organ position	Cumulative weighting factor
Cervical spine	1	1	1	1	2	1	7
Head	2	1	1	2	1	1	8
Thorax	2	3	2	1	2	2	12
Eye	2	2	2	1	3	2	12
Abdomen	3	3	3	2	3	2	16
Prostate	3	3	3	2	3	3	17

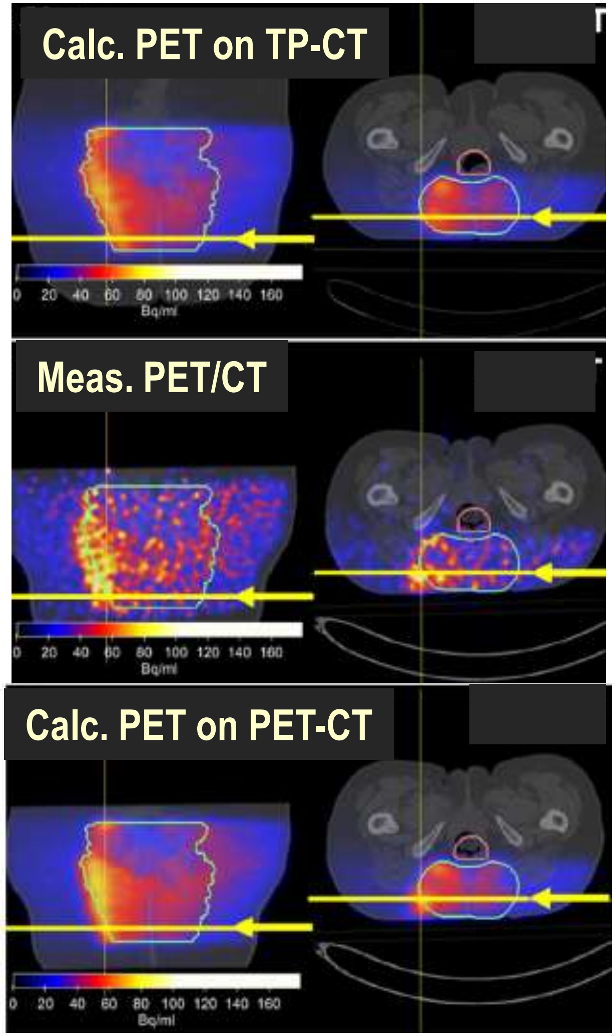
Parodi et al, IJROBP 68, 2007; Knopf, Parodi et al, PMB 54, 2009; Knopf, Parodi et al, IJROBP 72, 2011

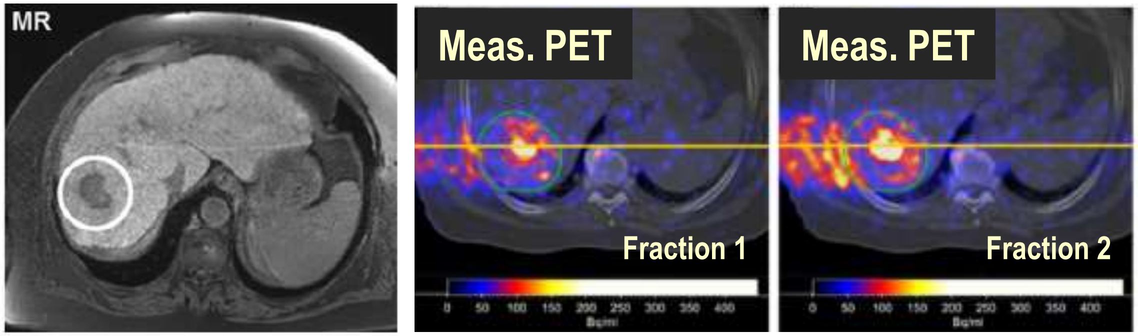
Clinical implementation (II): offline PET/CT

At HIT (p, ^{12}C) similar findings as MGH, moreover

- \+ Feasibility and reproducibility of shuttle transport
- \+ Enhanced signal in distal part of the field due to ^{11}C projectile fragments from ^{12}C ion beam
- \+ Feasibility of range monitoring also in extracranial sites, detection of mispositioning
- \+ Enhanced signal in necrotic areas („markers“)
- \- Even lower counting statistics for ^{12}C ions than *p*
- \- Challenges of 4D gated imaging at low counts

Scanned ^{12}C ions





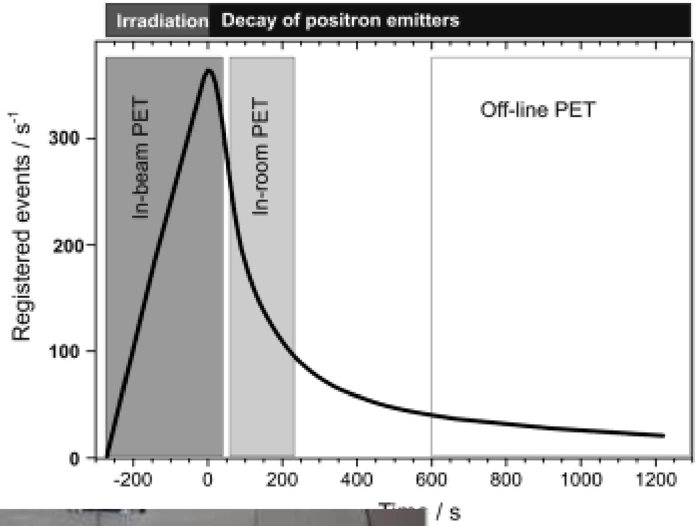
Scanned ^{12}C ions

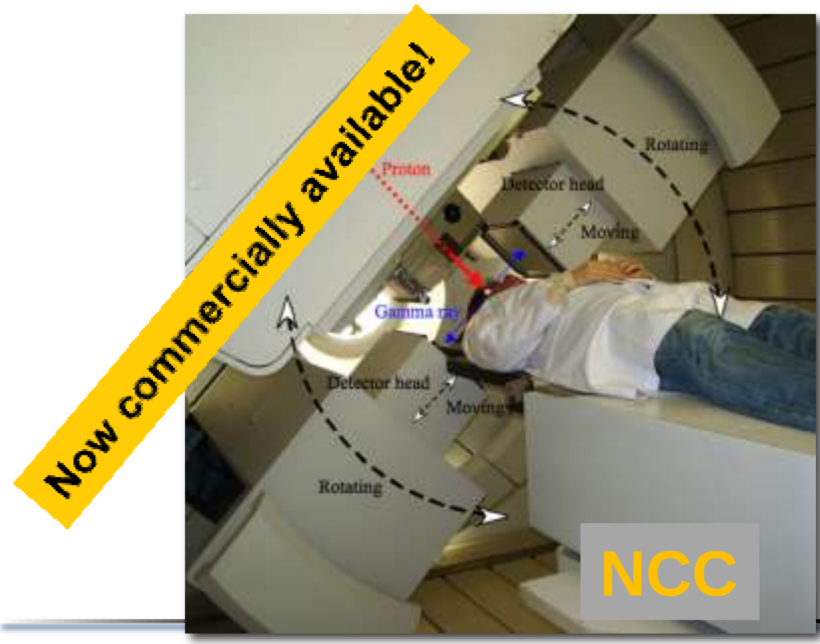
Bauer et al, Radiother Oncol 2013, Kurz et al, Radiother Oncol 2012

Clinical implementation (III): in-room

In-room PET

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





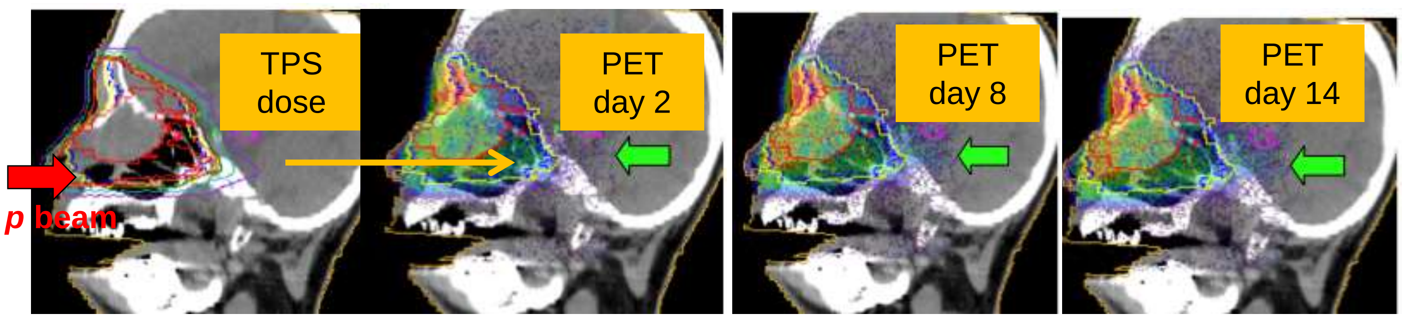
Nishio et al IJROBP 2010, Zhou et al PMB 2011, Shakirin et al PMB 2011, Min et al IJROBP 2013

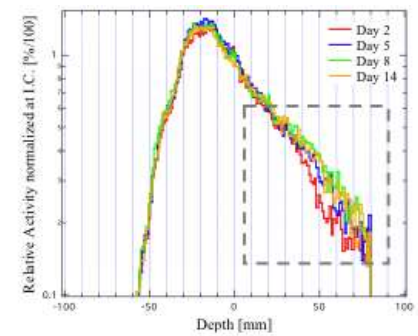
Clinical implementation (III): in-room PET

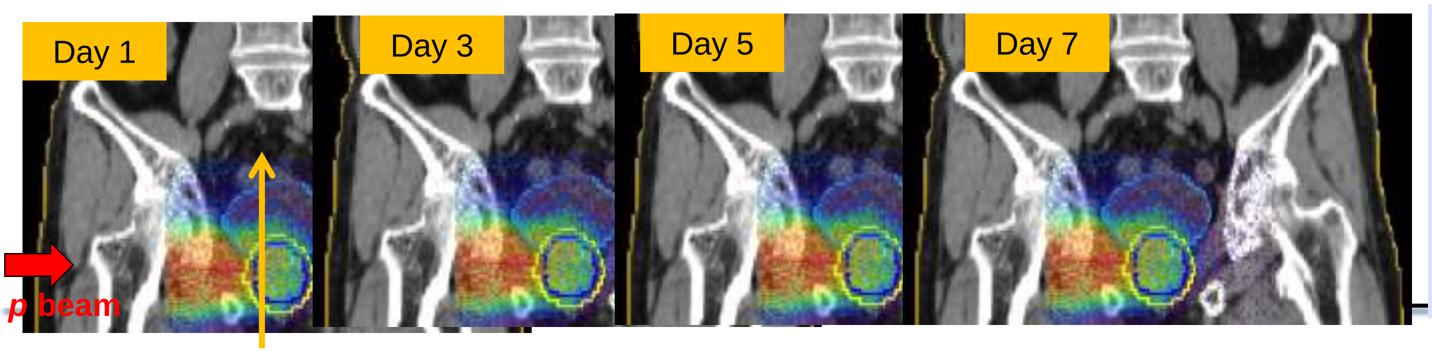
Experience from dual-head in-room PET at NCC Kashiwa (p)

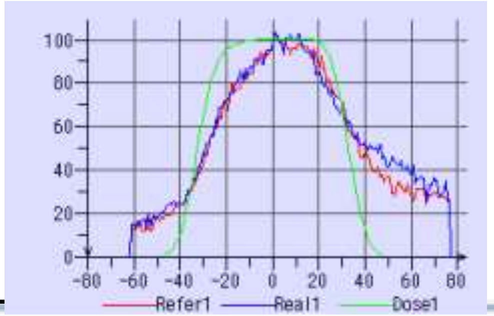
+ 200 s acquisition after end of irradiation found sufficient for imaging
+ Detection of inter-fractional delivery / anatomy changes
○ Assessment of reproducibility (daily activity compared to reference meas.)
- Small planar system optimised for animal imaging, limited FOV
- No acquisition possible during beam-on time

Scattered protons









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

Clinical implementation (III): in-room PET

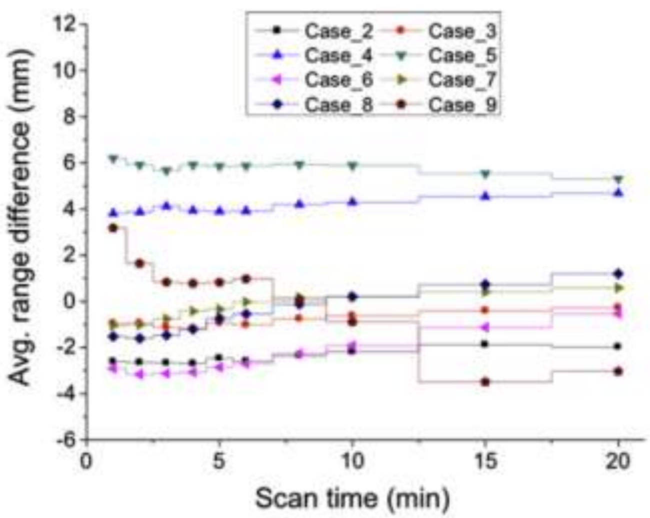
Experience from full-ring in-room PET at MGH (p)

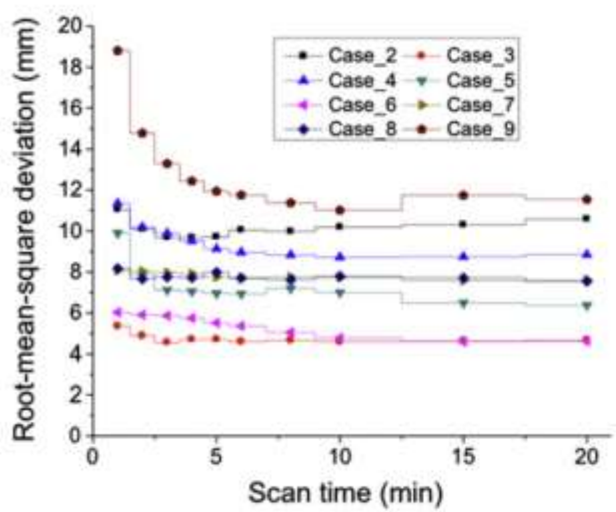
\+ 5 min measurement started 2 min after irradiation end similar to 20 min scan

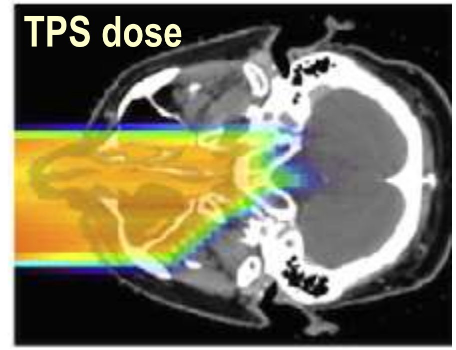
\+ Range agreement mostly within ±3 mm (4 - 11 mm rms)

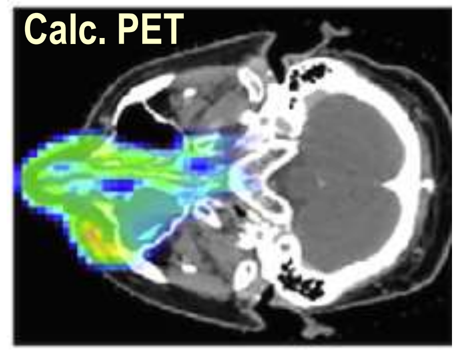
\- ~ 2 mm co-registration errors despite robotic couch and radioactive markers

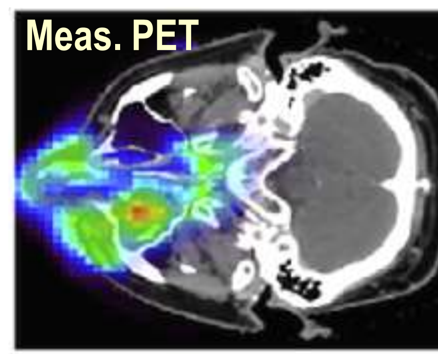
\- Limited bore of scanner (only head and pediatric cases)











Zhou et al PMB 2011, Min et al IJROBP 2013

R&D challenges

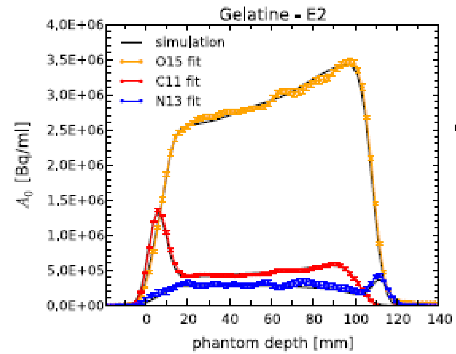
Remaining limitations of PET-based verification

- 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

Modeling of PET prediction

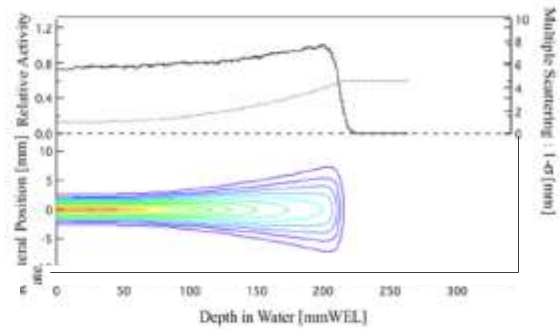
Ongoing efforts to

- Improve MC prediction via experimental based adjustement of β+ activation cross sections (only feasible for *p*)
- Speed up calculation with analytical approaches, ideally using same pencil beam algorithms as TPS
- Overcome limitations of CT-based tissue classification by using MRI information or Dual Energy CT

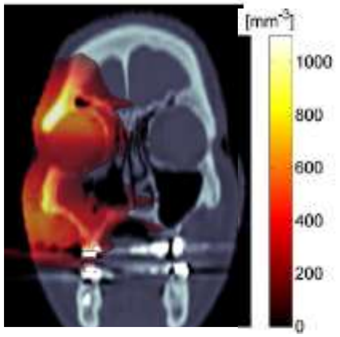


Bauer, .., Parodi, PMB 2013

TH-C-144-12

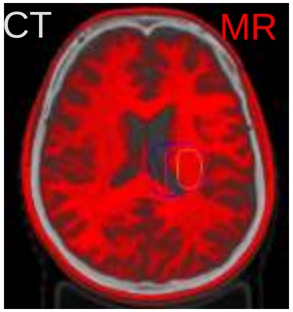


Mitayake et al, MP 2011



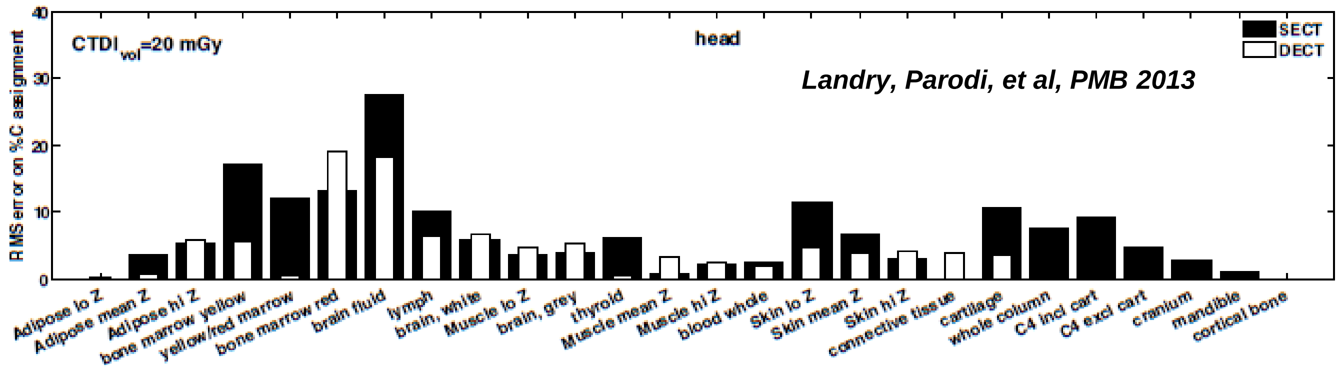
Frey et al, submitted to PMB

TH-C-144-6



Bauer et al,
In preparation

WE-G-500-6

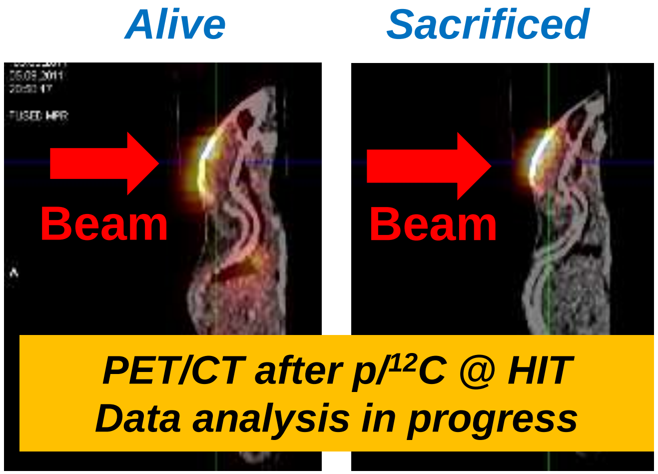


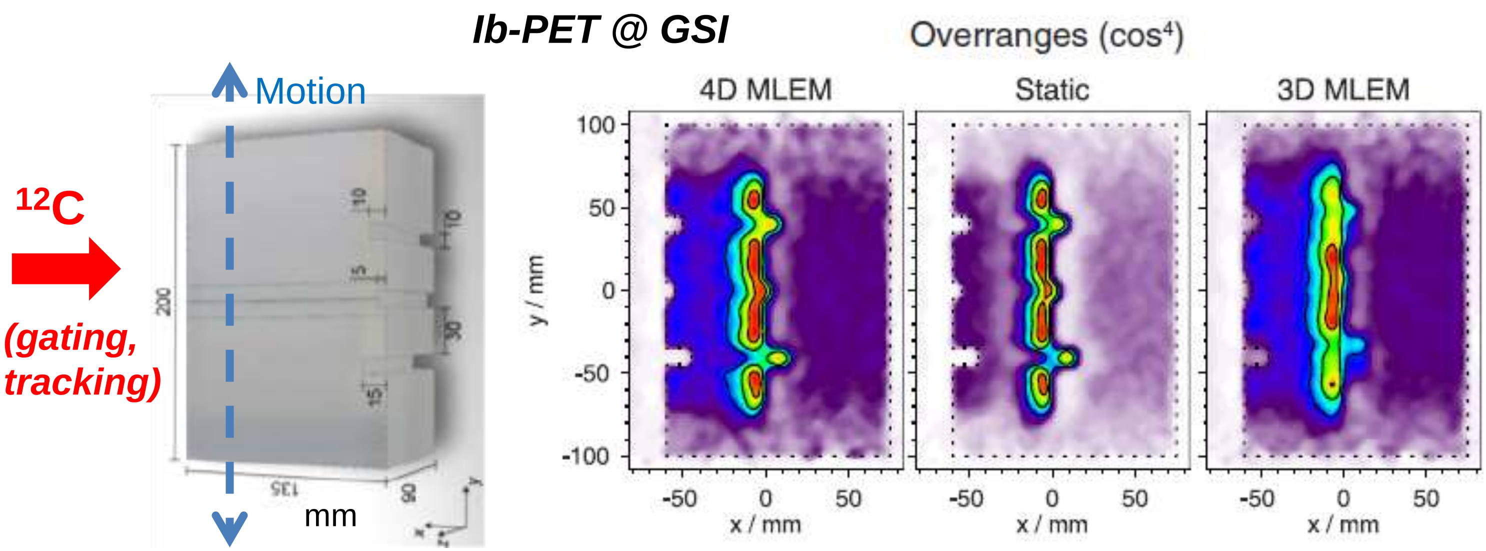
Landry, Parodi, et al, PMB 2013

Washout and motion blurring

Ongoing efforts to

- Improve washout modeling on the basis of animal studies
- Assess experimentally the potential and limitations of time-resolved 4D PET for monitoring motion-compensated delivery at different facilities and PET installations





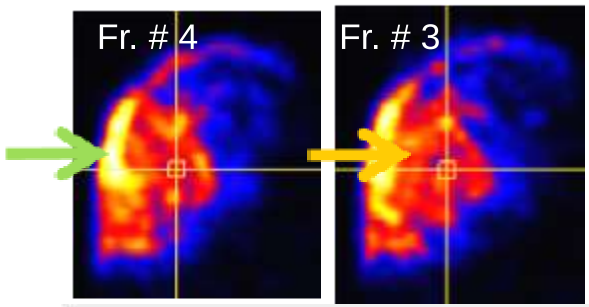
Stützer et al, PMB 2013

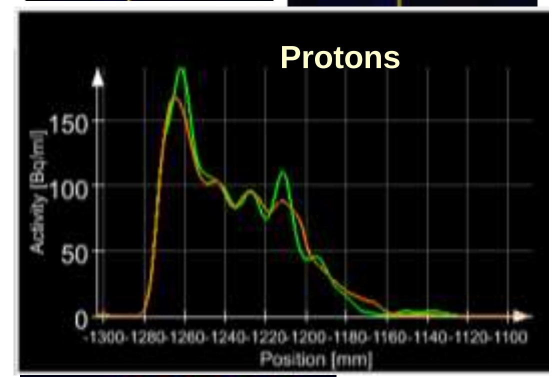
Automated range assessment

Ongoing efforts to establish

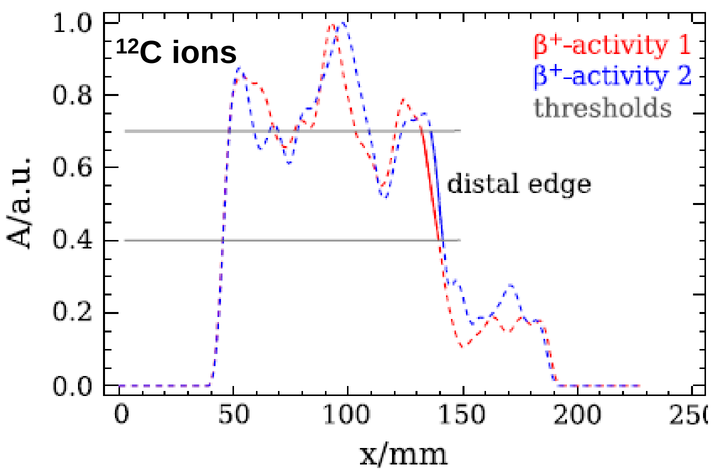
- Robust, automated range assessment from PET distributions based on profile shift analysis or % fall-off in BEV *(meas. vs calc., meas. vs meas.)*

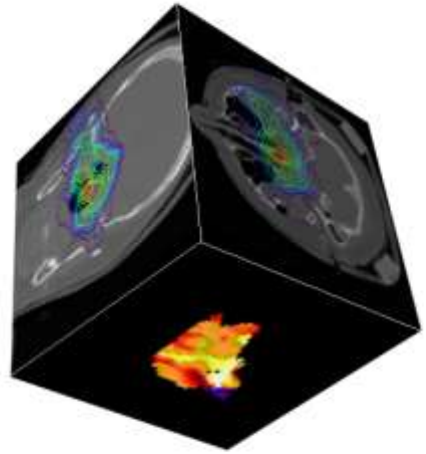
Offline PET/CT @ HIT



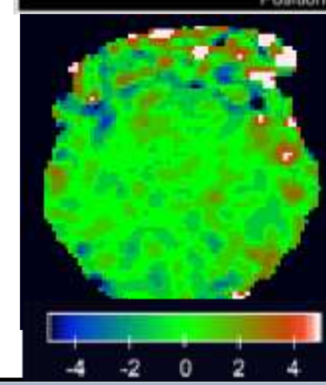


In-beam PET @ GSI





Helmbrecht et al, PMB 2012



Range shift in mm

Similar approach for in-room PET @ MGH (Min et al, IJROBP 2013)

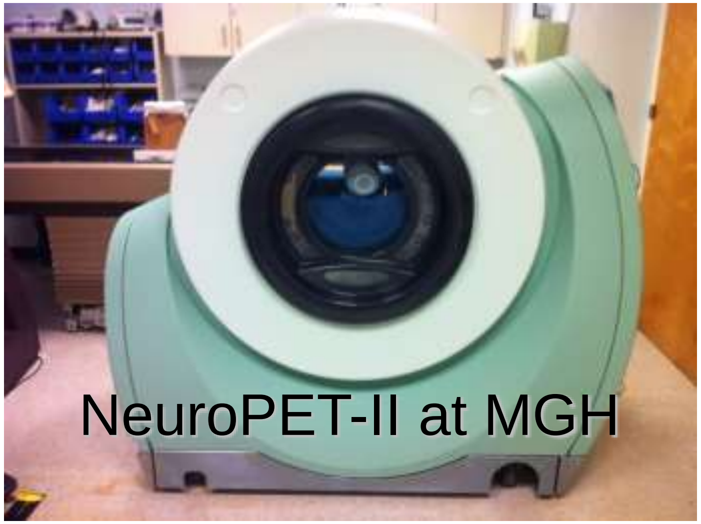
- Decision support system for clinical workflow

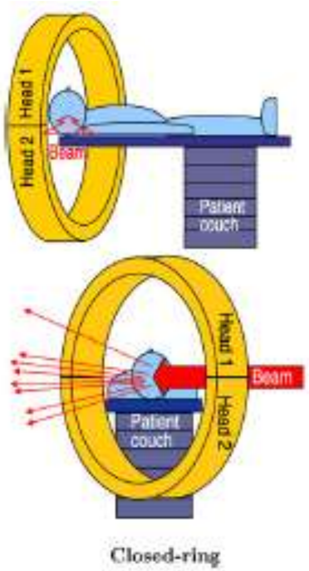
Unholtz, …, Parodi, IEEE MIC Conf. Rec. 2011

Hardware improvements

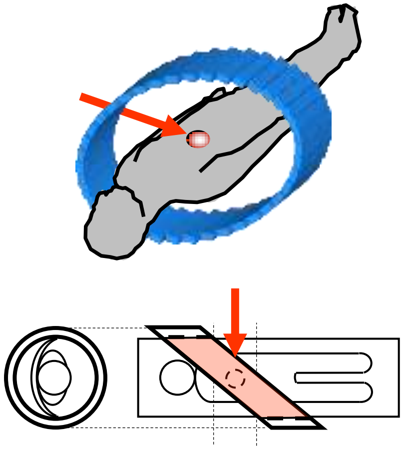
Full ring solutions

- Prototype small bore PET/CT scanner being commissioned at MGH prior to clinical usage
- Small scale in-beam full ring scanner prototypes being developed and tested with stable and radioactive beams at NIRS

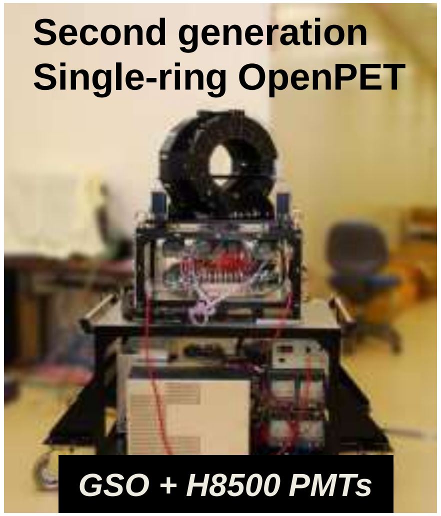




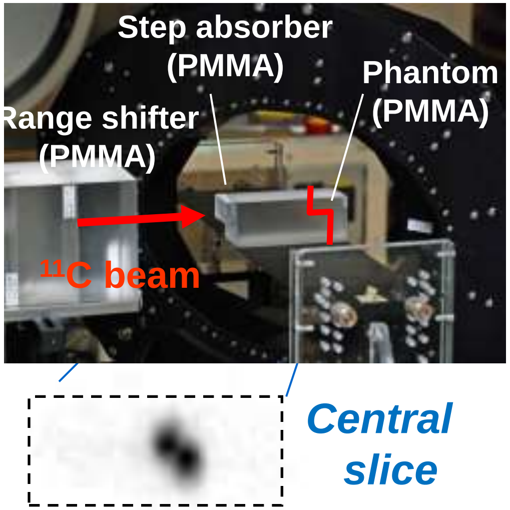
Crespo et al, PMB 2007



Tashima PMB 2012



Yamaya IEEE MIC 2012, paper in prep.



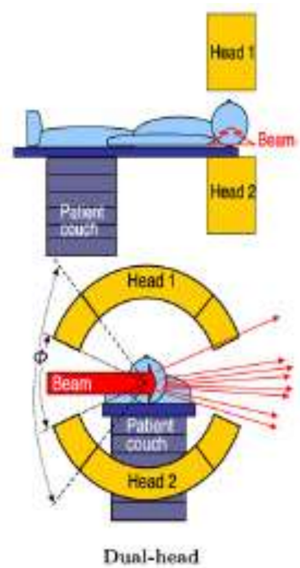
Yamaya, paper in prep.

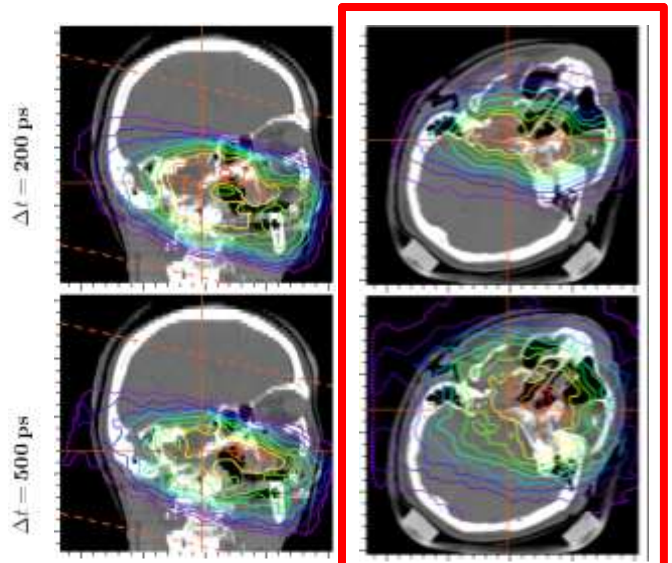
Images courtesy of H. Paganetti, MGH Boston, and Taiga Yamaya, NIRS Japan

Hardware improvements

Dual head solutions

- New detector developments towards ultra-fast Time-of-Flight (TOF) in-beam PET
- Small scale in-beam prototypes being developed and tested

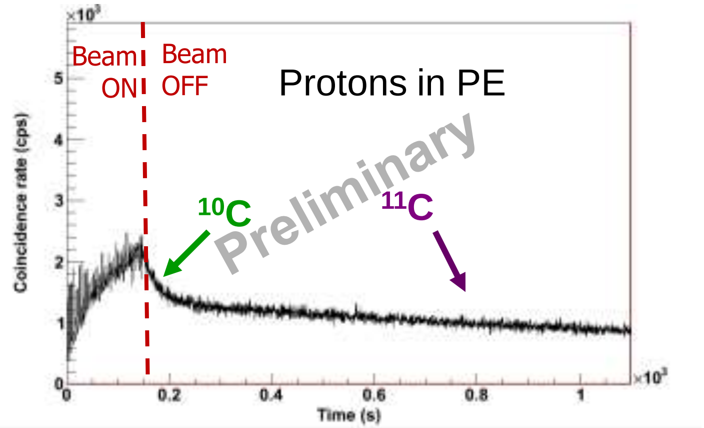




Crespo et al, PMB 2007

Experimental set-up of TU-Delft group @ HIT

Philips dSiPM and LYSO crystals



Cambraia Lopes et al, to be presented at IEEE MIC 2013

Images courtesy of D. Schaart and P. Cambraia Lopes, TU Delft

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**

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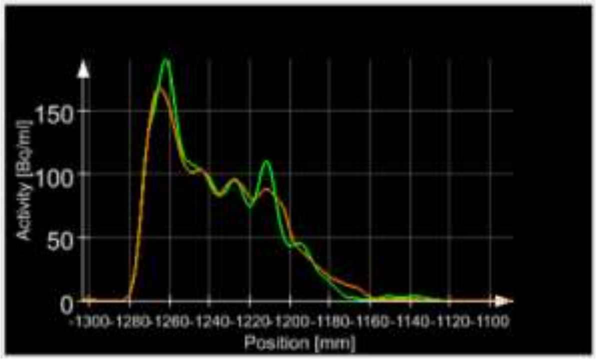
D.R. Schaart, P. Cambraia, TU Delft, The Netherlands

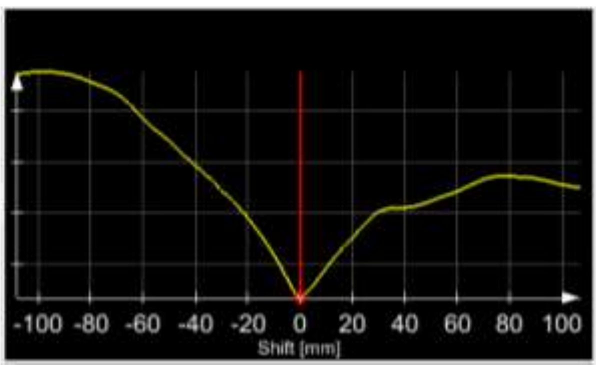
P. Crespo, LIP Portugal

Thank you for your attention

Automated range assessment

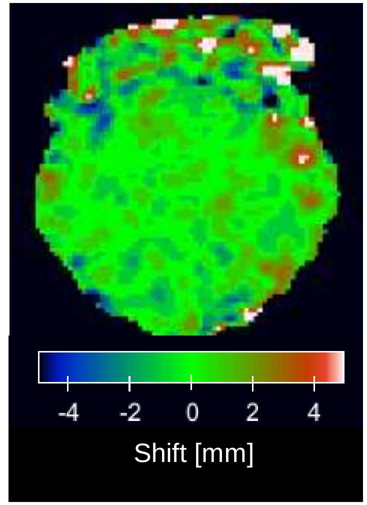
Profile shift analysis [*] or % fall-off in BEV

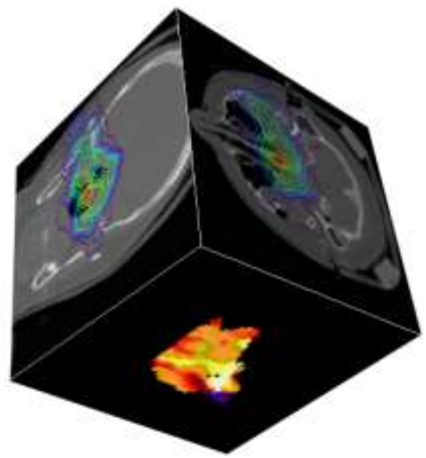




[*] *Knopf, Parodi et al, PMB 2008*

PET difference

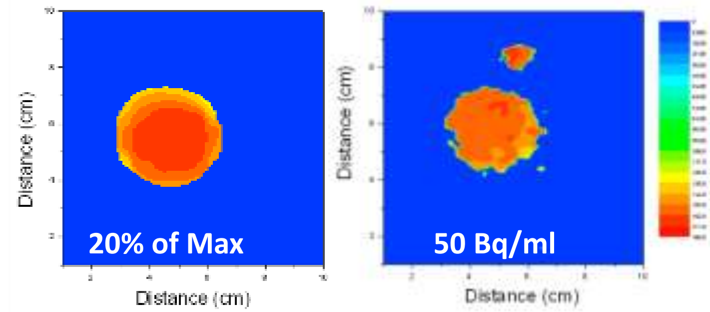




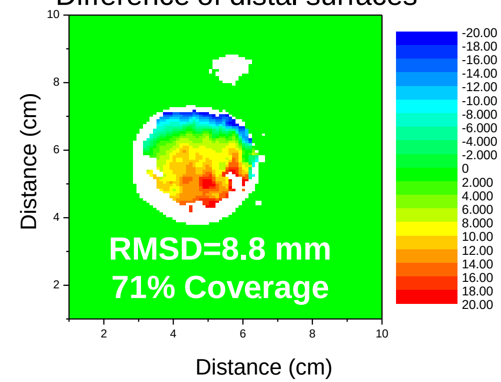
PET – Dose difference

Distal Surface_Dose

Distal Surface_PET



Difference of distal surfaces

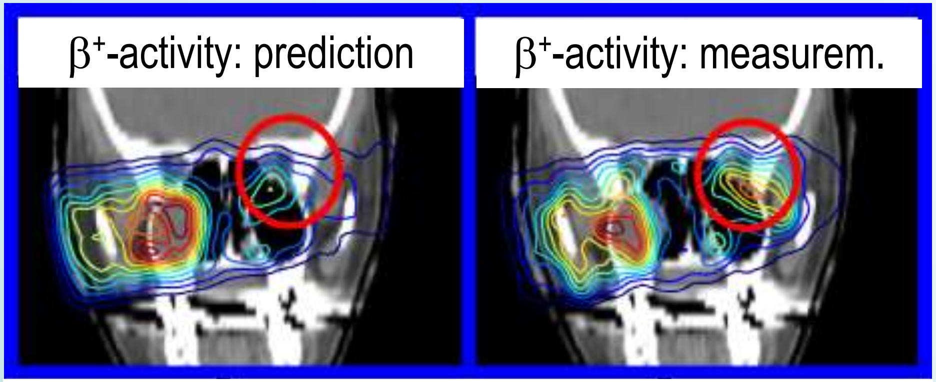


Courtesy of H. Paganetti and C.H. Min MGH

Unholtz, Bauer, …, Parodi, IEEE MIC CR 2011, Helmbrecht et al, PMB 2012

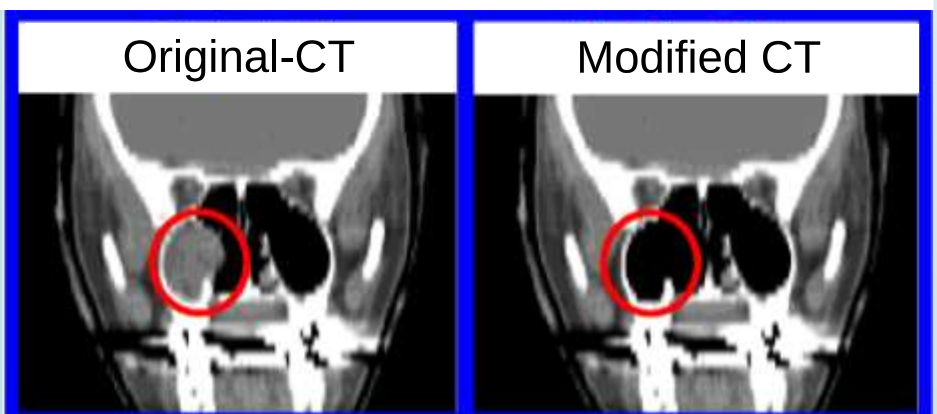
Indirect PET-guided dose quantification

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

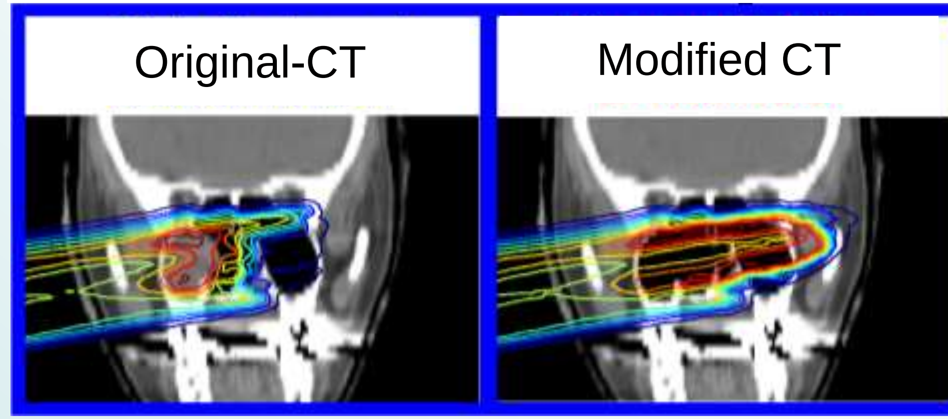


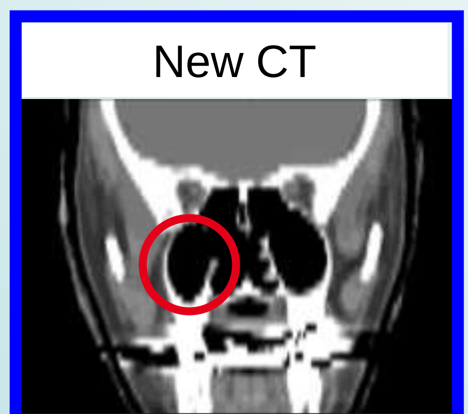
Hypothesis on the reason for the deviation from the treatment plan

Interactive CT manipulation



Dose recalculation

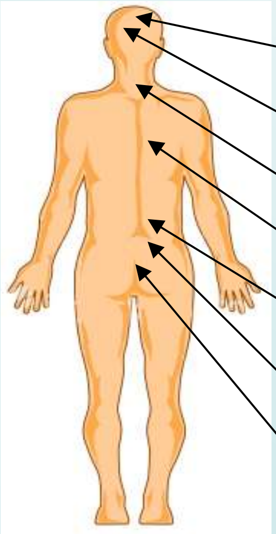




CT after
PET findings

Parodi Ph.D. Thesis, 2004; Enghardt, Parodi et al, Radiother Oncol, 2004

Offline PET/CT clinical experience at MGH

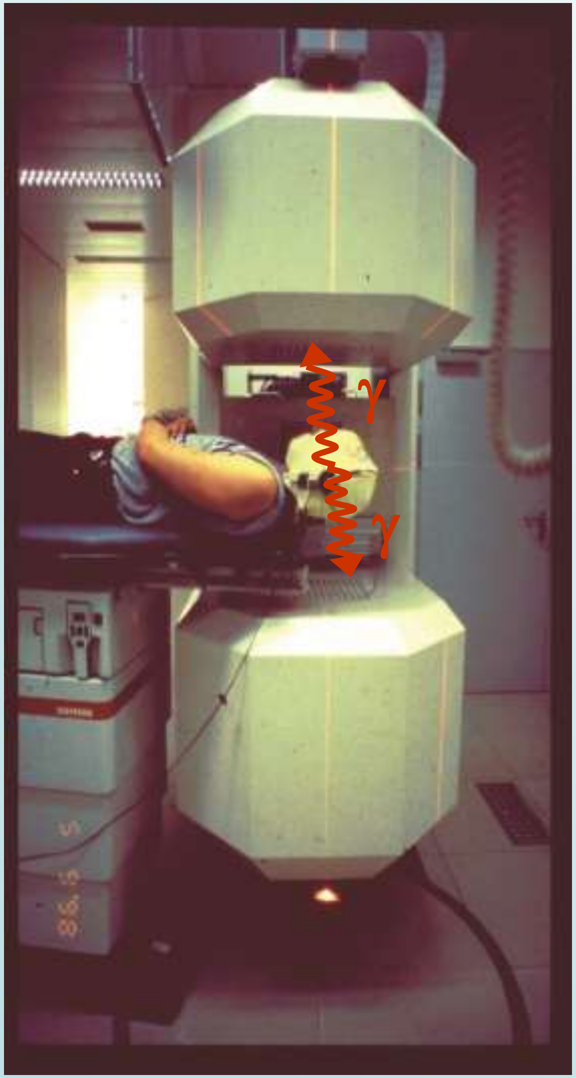


	# of patients	Dose / field [GyE]
head	12	0.9-3
eye	1	10
C-spine	3	0.6-2.5
T-spine	1	1.8
L-spine	2	0.9-2
sacrum	2	1-2
prostate	2	2
TOTAL	**23**	**0.6-10**

	Challenge						
Tumor location	Biologic washout	Motion	MC uncertainties	Beam direction	CT fusion	Organ position	Cumulative weighting factor
Cervical spine	1	1	1	1	2	1	7
Head	2	1	1	2	1	1	8
Thorax	2	3	2	1	2	2	12
Eye	2	2	2	1	3	2	12
Abdomen	3	3	3	2	3	2	16
Prostate	3	3	3	2	3	3	17

Parodi et al, IJROBP 68, 2007; Knopf, Parodi et al, PMB 54, 2009; Knopf, Parodi et al, IJROBP 72, 2011

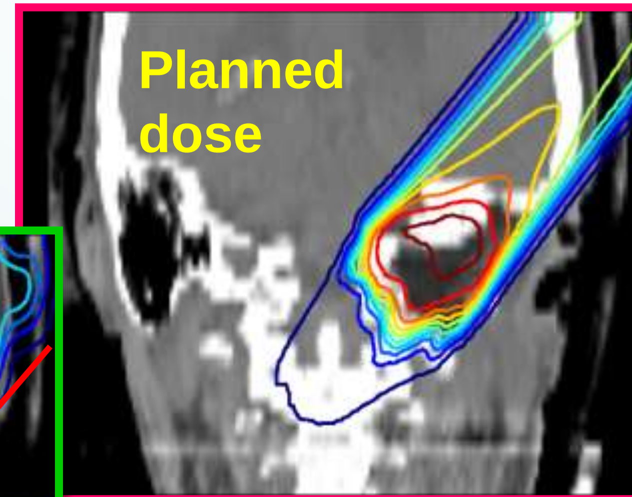
In-beam PET for ^{12}C ion therapy at GSI

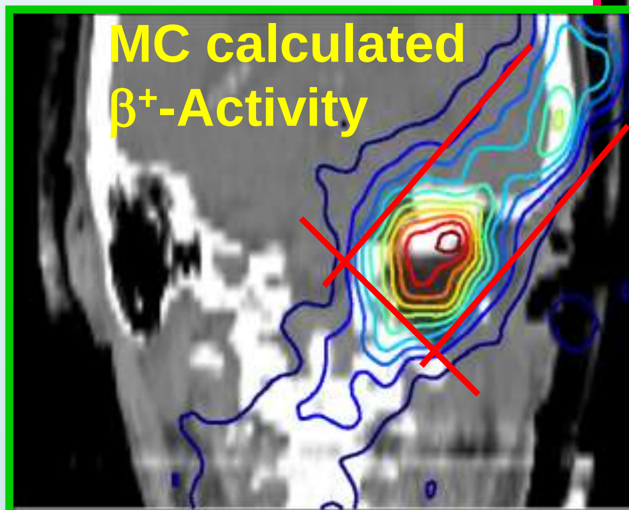


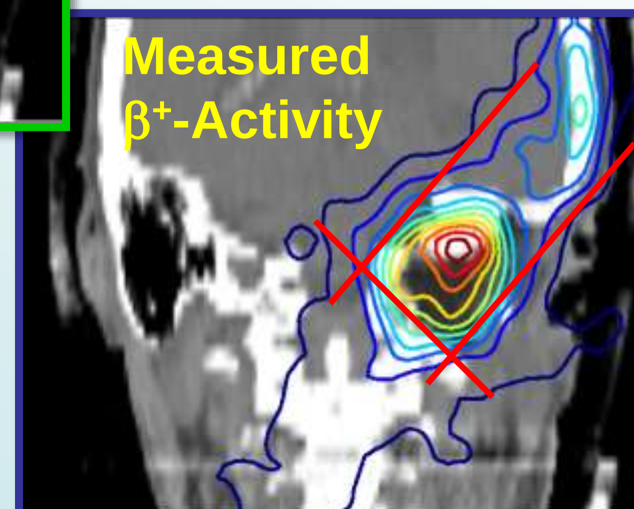
> 400 patients

For every fraction
(typically 20 d @ 1Gy)

Once







Verification of

- Beam range
- Lateral position

In case of deviation

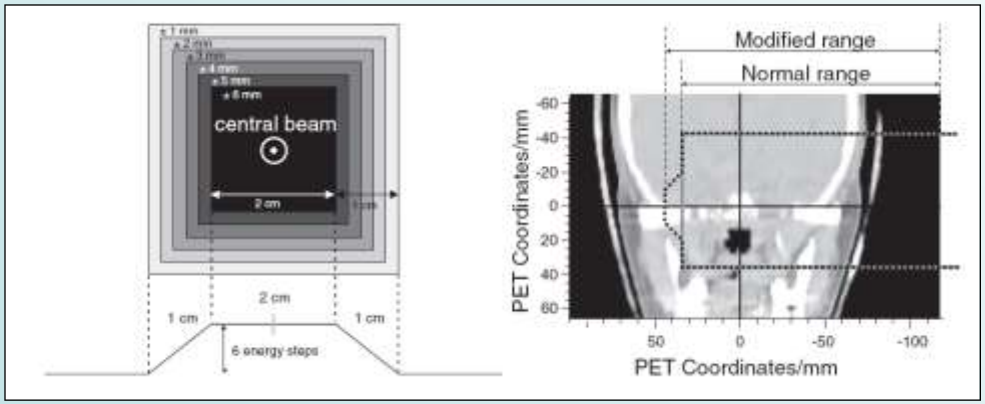
- Timely reaction

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

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 %