Opportunities and challenges in particle radiotherapy

Katia Parodi, Ph.D.
Ludwig-Maximilians-Universität München (LMU Munich)
Department of Medical Physics, Munich, Germany

61st AAPM Annual Meeting

AAPM 2019 JUL 14–18

San Antonio, July 15th, 2019

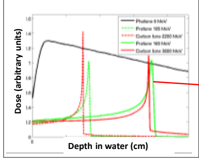
Conflict of Interest

Research collaboration and two license agreements with RaySearch Laboratories AB

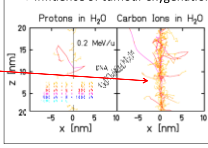
RaySearch Laboratories

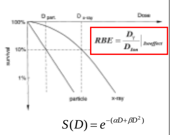
Physical and biological rationale of ion beam therapy

Physical selectivity
- Depth-dose profile (Bragg-Peak)
- ↓ lateral scattering *(Z>1)*



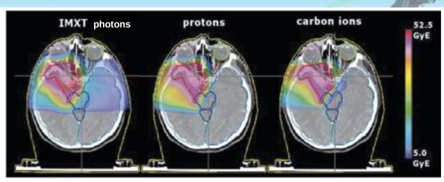
Biological Effectiveness ***Optimal differential effect at Z ≈ 6***
- Elevated local ionization density
- ↑ Relative Biological Effectiveness (RBE)
- ↓ Influence of tumour oxygenation (OER)





Parodi Habil Thesis 2008 · Krämer et al, Adv Space Res 1994 · Kraft Prog Part Nucl Phys 2000

Clinical rationale of ion beam therapy

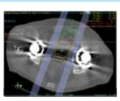


Is what we see what the patient receives?

Nuclear Physics for Medicine Report, NUPECC, 2014

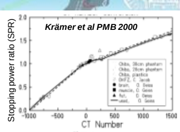
Treatment (re)planning uncertainties

Patient model
- Metal artifacts
- Image quality (CBCT)
- HU-SPR conversion
- Tissue-dependent biological parameters

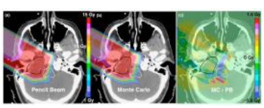


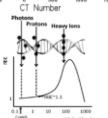
Giantsoudi et al, PMB 2017

University Hospital, LMU



Dose calculation
- Beam model
- Tissue heterogeneities
- Biological models



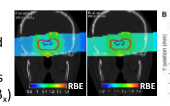


Schuemann et al, MedPhys 2017, Special issue PT · Willers et al, Radiother Oncol 2018

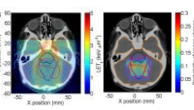
Treatment (re)planning uncertainties

RBE models in treatment planning

Protons
- Constant RBE = 1.1 clinically used
- Known RBE variations with LET
- Uncertainties of different models (typically based on LET_D and α_x/β_x)
- Unclear correlation to outcome

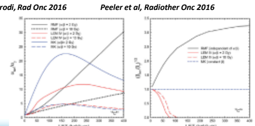


Giovannini...Mairani, Parodi, Rad Onc 2016

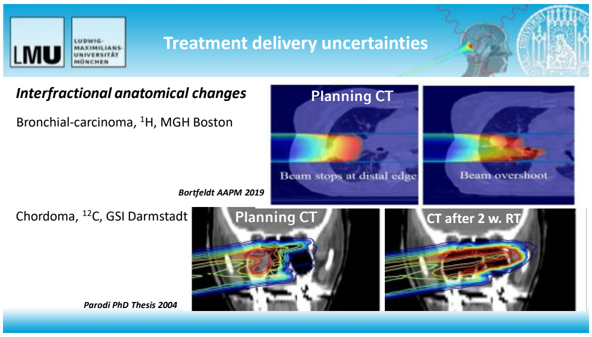


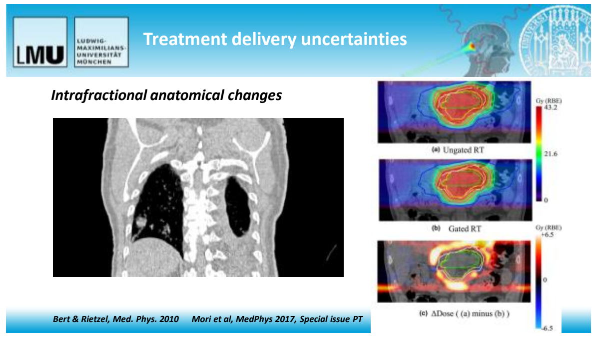
Peeler et al, Radiother Onc 2016

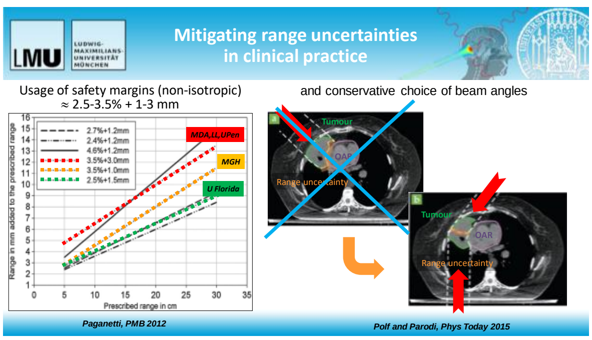
Carbon ions
- Variable RBE scheme (accounting for mixed field)
- Different models used in the clinics (LEM, MKM) based on different underlying assuptions
- Uncertainties of model predictions
- Unclear correlation to outcome

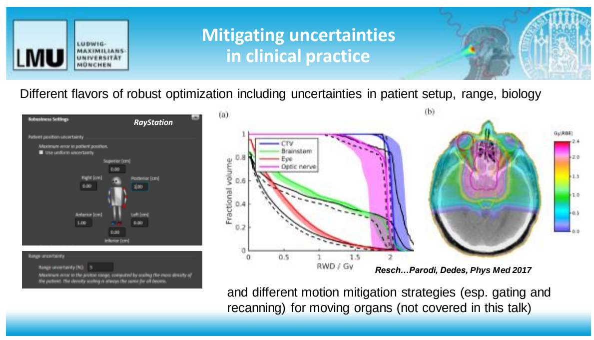


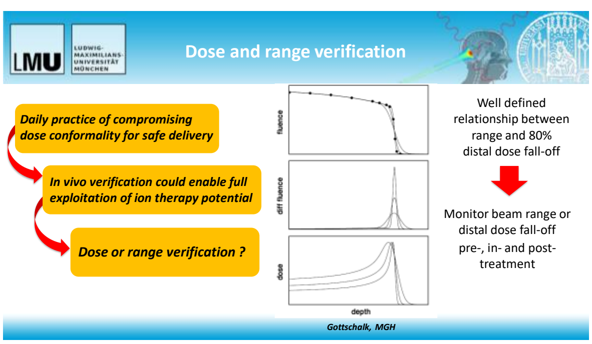
Stewart...Scholz, MedPhys 2017, Special issue PT

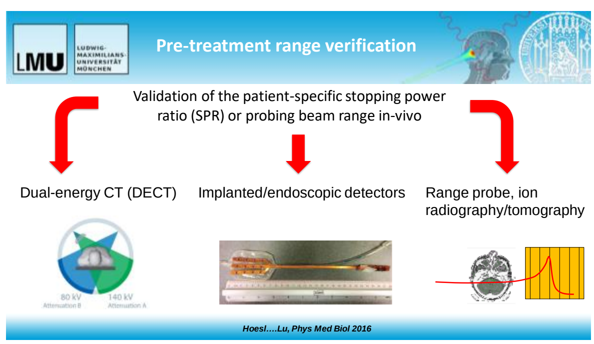

LMU
LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN
Treatment delivery uncertainties
Interfractional anatomical changes
Bronchial-carcinoma, 1H, MGH Boston
Planning CT
Beam stops at distal edge
Beam overshoot
Bortfeldt AAPM 2019
Chordoma, 12C, GSI Darmstadt
Planning CT
CT after 2 w. RT
Parodi PhD Thesis 2004

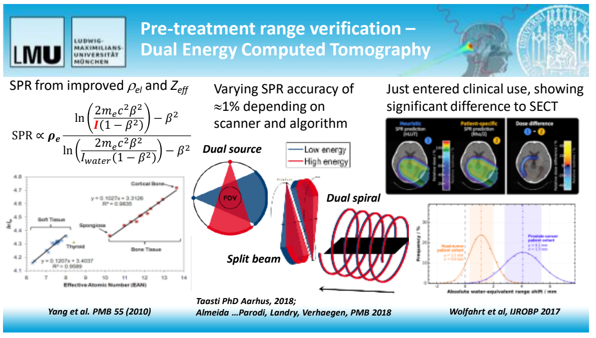

LMU
LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN
Treatment delivery uncertainties
Intrafractional anatomical changes
(a) Ungated RT
(b) Gated RT
(c) ΔDose ((a) minus (b))
Bert & Rietzel, Med. Phys. 2010
Mori et al, MedPhys 2017, Special issue PT

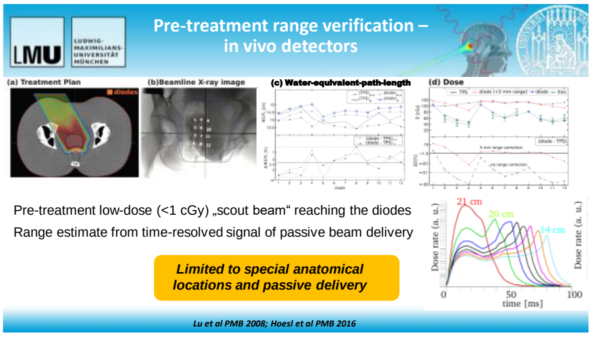

LMU
LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN
Mitigating range uncertainties
in clinical practice
Usage of safety margins (non-isotropic)
≈ 2.5-3.5% + 1-3 mm
and conservative choice of beam angles
2.7%+1.2mm
2.4%+1.2mm
4.6%+1.2mm
3.5%+3.0mm
3.5%+1.0mm
2.5%+1.5mm
MDA,LL,UPen
MGH
U Florida
Range in mm added to the prescribed range
Prescribed range in cm
Tumour
OAR
Range uncertainty
Paganetti, PMB 2012
Polf and Parodi, Phys Today 2015

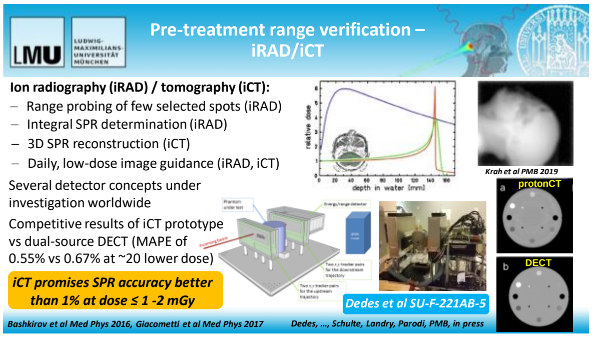

LMU
LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN
Mitigating uncertainties
in clinical practice
Different flavors of robust optimization including uncertainties in patient setup, range, biology
RayStation
CTV
Brainstem
Eye
Optic nerve
Fractional volume
RWD / Gy
Resch...Parodi, Dedes, Phys Med 2017
and different motion mitigation strategies (esp. gating and recanning) for moving organs (not covered in this talk)

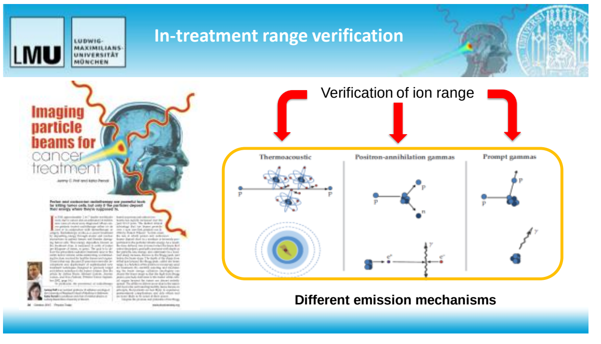

LMU
LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN
Dose and range verification
Daily practice of compromising dose conformality for safe delivery
In vivo verification could enable full exploitation of ion therapy potential
Dose or range verification ?
fluence
diff fluence
dose
depth
Well defined relationship between range and 80% distal dose fall-off
Monitor beam range or distal dose fall-off
pre-, in- and post-treatment
Gottschalk, MGH

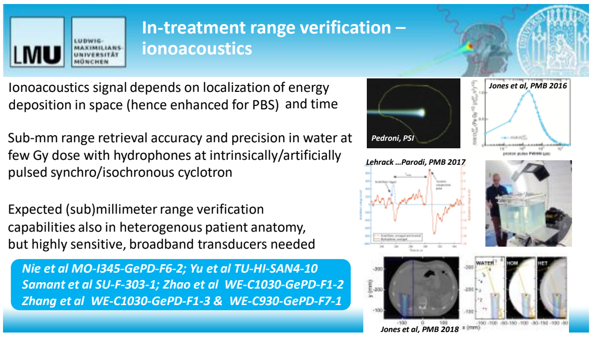

LMU
LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN
Pre-treatment range verification
Validation of the patient-specific stopping power ratio (SPR) or probing beam range in-vivo
Dual-energy CT (DECT)
Implanted/endoscopic detectors
Range probe, ion radiography/tomography
80 kV
140 kV
Hoesl....Lu, Phys Med Biol 2016

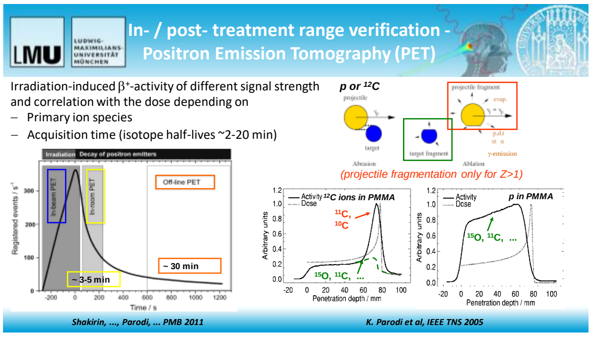

Pre-treatment range verification –
Dual Energy Computed Tomography
SPR from improved ρ_{el} and Z_{eff}
$$\mathrm{SPR} \propto \rho_e \frac{\ln\left(\frac{2m_ec^2\beta^2}{I(1-\beta^2)}\right)-\beta^2}{\ln\left(\frac{2m_ec^2\beta^2}{I_{water}(1-\beta^2)}\right)-\beta^2}$$
Varying SPR accuracy of ≈1% depending on scanner and algorithm
Just entered clinical use, showing significant difference to SECT
Dual source
Low energy
High energy
Dual spiral
Split beam
Effective Atomic Number (EAN)
Absolute water-equivalent range shift / mm
Yang et al. PMB 55 (2010)
Taasti PhD Aarhus, 2018;
Almeida …Parodi, Landry, Verhaegen, PMB 2018
Wolfahrt et al, IJROBP 2017


Pre-treatment range verification –
in vivo detectors
(a) Treatment Plan
(b)Beamline X-ray image
(c) Water-equivalent-path-length
(d) Dose
Pre-treatment low-dose (<1 cGy) „scout beam" reaching the diodes
Range estimate from time-resolved signal of passive beam delivery
Limited to special anatomical locations and passive delivery
21 cm
20 cm
14 cm
Dose rate (a. u.)
time [ms]
Lu et al PMB 2008; Hoesl et al PMB 2016


Pre-treatment range verification –
iRAD/iCT
Ion radiography (iRAD) / tomography (iCT):
– Range probing of few selected spots (iRAD)
– Integral SPR determination (iRAD)
– 3D SPR reconstruction (iCT)
– Daily, low-dose image guidance (iRAD, iCT)
Several detector concepts under investigation worldwide
Competitive results of iCT prototype vs dual-source DECT (MAPE of 0.55% vs 0.67% at ~20 lower dose)
iCT promises SPR accuracy better than 1% at dose ≤ 1 -2 mGy
relative dose
depth in water [mm]
Krah et al PMB 2019
protonCT
DECT
Dedes et al SU-F-221AB-5
Bashkirov et al Med Phys 2016, Giacometti et al Med Phys 2017
Dedes, …, Schulte, Landry, Parodi, PMB, in press


In-treatment range verification
Imaging particle beams for cancer treatment
Verification of ion range
Thermoacoustic
Positron-annihilation gammas
Prompt gammas
Different emission mechanisms


In-treatment range verification –
ionoacoustics
Ionoacoustics signal depends on localization of energy deposition in space (hence enhanced for PBS) and time
Sub-mm range retrieval accuracy and precision in water at few Gy dose with hydrophones at intrinsically/artificially pulsed synchro/isochronous cyclotron
Expected (sub)millimeter range verification capabilities also in heterogenous patient anatomy, but highly sensitive, broadband transducers needed
Nie et al MO-I345-GePD-F6-2; Yu et al TU-HI-SAN4-10
Samant et al SU-F-303-1; Zhao et al WE-C1030-GePD-F1-2
Zhang et al WE-C1030-GePD-F1-3 & WE-C930-GePD-F1-1
Pedroni, PSI
Jones et al, PMB 2016
Lehrack …Parodi, PMB 2017
Jones et al, PMB 2018

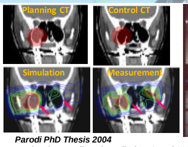

In- / post- treatment range verification -
Positron Emission Tomography (PET)
Irradiation-induced β⁺-activity of different signal strength and correlation with the dose depending on
– Primary ion species
– Acquisition time (isotope half-lives ~2-20 min)
p or ¹²C
(projectile fragmentation only for Z>1)
Irradiation
Decay of positron emitters
In-beam PET
In-room PET
Off-line PET
~ 3-5 min
~ 30 min
Registered events / s
Time / s
Activity ¹²C ions in PMMA
Dose
¹¹C, ¹⁰C
¹⁵O, ¹¹C, …
Penetration depth / mm
Arbitrary units
p in PMMA
Activity
Dose
¹⁵O, ¹¹C, …
Shakirin, …, Parodi, … PMB 2011
K. Parodi et al, IEEE TNS 2005

In-treatment range verification – In-beam PET

First clinical experience based on instrumentation adapted from nuclear medicine

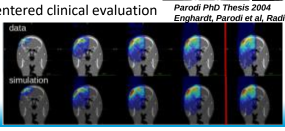
Feasibility to detect inter-fractional changes (anatomy, positioning) despite low SNR, biological washout and not yet optimal instrumentation

Next-generation dedicated detectors able of dynamic imaging just entered clinical evaluation



Parodi PhD Thesis 2004
Enghardt, Parodi et al, Radiother Oncol 2004

Fiorina…Bisogni, Phys Med 2018

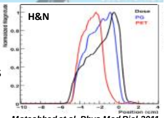


In-treatment range verification – Prompt gamma (PG)

Fast (sub-ns) emission eliminates issue of biological washout

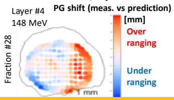
Signal fall-off is closely correlated to Bragg peak position due to lower cross section thresholds than for PET

Dedicated developments for directional detection of high energy PGs (≈ 2-7 MeV) embedded in huge neutron background



Moteabbed et al, Phys Med Biol 2011

Prototype 1D PG camera with slit collimators



Shift retrieval accuracy of 2mm

Smeets et al Phys Med 2012, Xie et al IJROBP 2017, Courtesy Kevin Teo, UPENN

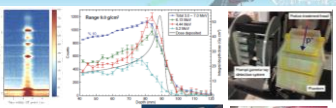
In-treatment range verification – Prompt gamma (PG)

Prompt gamma spectroscopy

– Exploits PG energy information
– Custom-made collimated prototype close to start pilot clinical study @ MGH

Verburg et al, PMB 2013 Hueso-González et al, PMB 2018

Verburg et al WE-HI-SAN2-6



Prompt gamma timing

– Exploits timing information, overcoming collimation
– Custom-made prototype under development for future clinical translation @ Oncoray Dresden

Golnik et al PMB 2014; Pausch et al, PMB 2018; Werner…Pausch, P

Compton camera imaging

– Exploits Compton kinematics, overcoming collimation
– Commercial prototype under further development for future clinical translation @ Maryland

Draeger…Polf, PMB 2018

Panthi et al MO-I345-GePD-F6-5

Post-treatment range verification – Offline PET and MRI

Data acquisition after irradiation @ offline diagnostic scanners

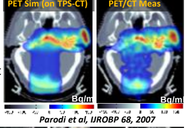
PET(/CT)

MRI

Post-treatment range verification – Offline PET and MRI

Offline PET(/CT) imaging

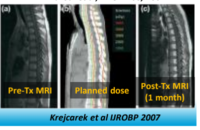
- Exploits long-lived emitters contribution (e.g., ^{11}C)
- Requires long acquisition time and accurate co-registration of treatment/imaging positions
- Suffers from signal loss/degradation from physical/biological washout
- Can provide reliable information only in low-perfused, C-rich regions



Parodi et al, IJROBP 68, 2007

Offline MRI imaging

- Exploits MRI changes due to physiological processes (e.g. fatty replacement of irradiated bone marrow)
- Onset on typical time scales of several fractions / entire treatment
- So far restricted to limited mechanisms in spine and liver
- Challenged by patient-specific variability



Krejcarek et al IJROBP 2007

Conclusion & Outlook

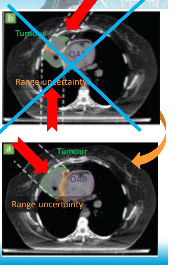
Treatment planning strategies can account for physical and biological uncertainties, however compromising achievable dose conformity

Additional studies needed to improve biological models

In vivo dose / range verification remains unmet challenge, although many approaches are possible before, during and after treatment

Promising techniques for in-vivo SPR assessment and real-time range verification are close to / just starting clinical translation & evaluation

Reduction of uncertainties at planning & delivery stage will enable more effective dose delivery and likely impact clinical outcome



Acknowledgement

Kevin Teo, University of Pennsylvania
David Carlson, University of Pennsylvania
Jonathan Farr, ADAM

Further reading:
Medical Physics Special Issue
"Current Challenges and Prospects in Particle Therapy"
(edited by J. Farr & K. Parodi, 2018)

Thank you for your attention