





Novel developments in imaging and dosimetry for Hadrontherapy

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Outline

Introduction to Particle Therapy
 The beam range monitor problem
 R&D in range monitoring
 Summary and conclusion

Tumor Control vs Tissue Complication

- Part of multi-disciplinary approach to cancer care
- Useful for 50-60% of all cancer patients (also together with surgery, chemotherapy)
- Can be given for cure or palliation
- Mainly used for locoregional treatment
- Benefits and sideeffects are usually limited to the area(s) being treated





The conventional RT

The photon (and e^-) beams are the most common in RT. Cheap, small, and reliable.

The energy release is not suitable to release dose in a deep tumor.

But the use of sophisticated imaging (CT), superposition of several beams, computer optimization, multi-leaves collimators and >40 year of R&D make IMRT effective and widespread

Dose-depth relation for γ and e^-









Particle therapy vs Photon RT

Photon beams are RT baseline. Hard competitors: small, reliable and not so expensive ->40 years R&D

- Beam penetration in tissue function of the beam energy
- Peak of dose released at the end of the track, sparing the normal tissue
- Accurate conformal dose to tumor with Spread Out Bragg Peak





Examples of Photons vs Particle saga...



Charged Particle Therapy in the world



Community looking at ⁴He – ¹⁶O beams: begin to be tested at clinical center

The range verification problem

AAPM, August 2012

Delegates were asked what they considered as the main obstacle to proton therapy becoming mainstream:

- 35 % unproven clinical advantage of lower integral dose
- 33 % range uncertainties
- 19 % never become a mainstream treatment option

RESEARCH

Aug 22, 2012 Will protons gradually replace photons?

The dose distribution advantages offered by proton therapy, particularly with the introduction of pencil-beam scanning, have stimulated increasing interest in this modality. But is the large capital expenditure required to build a proton therapy facility hindering the widespread implementation of this technique? And how big a problem is range uncertainty, which can prevent proton therapy from meeting its full potential?



Protons versus IMRT

Dose profiling in Particle Therapy

Why is so crucial to monitor the dose in particle therapy with respect to photon RT? It is like firing with machine-gun or using a precision rifle.. Inhomogeneities, metallic implants, CT artifact, HU conversion, inter session anatomical/physiological changes-> range variations

Effect of density changes in the target volume



Accounting for uncertainties in the clinical practice

Current approach: Opposed fields, overshooting



____[Tang et al. 2012]

Desirable approach: Different beam angles and no overshooting



Protons

Spec's of particle therapy monitor

In PT the beam is easily monitored in the transverse direction but longitudinally stops inside the patient. An ideal PT monitor device should measure the shape and (possibly) the absolute value of dose release fulfilling the following spec's:

- ✓ Measurements and feed-back should be provided during the treatment (in-beam). Even better if the monitor response can follow the irradiation scan on line
- Must relay on the signal by secondary particles, generated by the beam, that comes out from the patient
- Must deal with the background of the "non signal" secondaries that come out
- Must be embedded in a treatment room: space, reliability and "easy to run" issues are crucial

Beam secondaries.. Background or Signal?

Indicative secondary flux
emitted on full solid angle by ~150 MeV p beamIncident protons:1.0Photons0.3

Neutrons		0.15
rotons	G4 simulation	0.005
	Simalation	

The p, ${}^{12}C$ beams generate a huge amount of secondaries: prompt γs , PET- γs , neutrons and charged particles (in particular ${}^{12}C$ beam)

Can be used to track the tumor path inside the patient

How much are the nuclear models reliable? huge experimental and theoretical development effort ongoing to improve model and update MC



baseline dose monitoring in PT : PET

Baseline for monitor in PT is PET : autoactivation by hadron beam that creates β^+ emitters.

- Isotopes of short lifetime ¹¹C (20 min), ¹⁵O (2 min), ¹⁰C (20 s) with respect to conventional PET (hours)
- Low activity in comparison to conventional PET need quite long acquisition time (some minutes at minimum)
- Metabolic wash-out, the β^+ emitters are blurred by the patient metabolism

No direct space correlation between β^+ activity and dose release (but can be reliable computed by MC)



Correlation between β^+ activity and dose

Therapy beam	¹ H	³ He	⁷ Li	¹² C	¹⁶ O	Nuclear medicine
Activity density / Bq cm ⁻³ Gy ⁻¹	6600	5300	3060	1600	1030	10 ⁴ – 10 ⁵ Bq cm ⁻³

In a PT treatment are used much more p than ${}^{12}C$ (dose ~ Z^2)



In-Vivo range measurement with PET: workflow and potential W. Enghardt et al.: Radiother. Oncol. 73 (2004) S96



Problem to solve: Metabolic Washout! In-beam measurement is really necessary, but difficult. Trade-off: in-room or off-room measurement after irradiation (Heidelberg for example)







Courtesy of [sketch and exp. data taken from F. Le Foulher et al IEEE TNS 57 (2009), E. Testa et al, NIMB 267 (2009) 993. exp. Data reevaluated in 2012 with substantial corrections





- The gamma are quite copiously produced
 by proton and ¹²C beam by nuclear excitation.
- The emission region stretches along all
 the beam path but has been shown to ends near the Bragg peak for both beams.
- It's not simple backpointing the γ direction: the γ energy is in the 1-10
 MeV range-> much more difficult to stop and collimate with respect to ⁹⁹Tc 144 KeV γ in standard SPECT imaging
- Huge background (beam, energy and site specific) due to neutrons & uncorrelated γs produced by neutrons. TOF not easy to exploit in clinical practice



Pγ detectors: multi-slit approach



- Longitudinal prompt γ ray profiles at 2 mm level
- Selection of prompt-gamma events in TOF spectra
- energy cut: E_γ > 1100 keV



J. Krimmer et al. submitted to JINST

Courtesy of J. Krimmer (IPNL)

Influence of TOF on PG profiles (collimated cameras)



Roellinghoff PMB 2014





TOF : mandatory for carbon ions Not easy with clinical beam!!!

M. Pinto, submitted New J Phys Courtesy of D. Dauvergne

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Compton camera: Electronic collimation

>

$$\cos\varphi = 1 - m_0 c^2 \left(\frac{1}{E_{\gamma'}} - \frac{1}{E_{\gamma}}\right)$$

1

Based on γ Compton scattering: if known E_{γ} , measure $E_{\gamma'}$, \mathbf{r}_{γ} , $\mathbf{r}_{\gamma'} \rightarrow$ obtain f. But...

- E_γ not fixed → continuous γ spectra. Must be measured E_e
- γ' must be completely absorbed in the second detector
- Very good resolution needed on E_{γ,e} -> solid state detector. (must be fast!)
- [•] Difficult trade off between efficiency and resolution. Plenty of activity and countless groups and institutions !!





f e/h select cmd

- BGO 35 × 38 × 30 mm³
- 4 PMT





Compton camera: II

ENVISION Meeting Geneva 2014



Scatterer: CdZnTe, Absorber: Scint. (LSO, BGO) Scatterer: CdZnTe, Absorber: CdZnTe

CZT cross strip detector (20 × 20 × 5 mm³) Bruker Baltic, Riga





Biograph LSO block detector, 54 × 54 × 20 mm³ Siemens, Knoxville In-beam Compton imaging Tandetron of HZDR:

~1 MeV protons 4.44 MeV γ via ¹⁵N(*p*, *α*)¹²C

TU Dresden



SION





T. Kormoll, et al.: Nucl. Instrum. Meth. A626 (2011) 114, C. Golnik, et al.: IEEE NSS-MIC, Anaheim, 2012



Designed and assembled by IBA, in collaboration with Politechnic Milano.

Benchmarking against alternative detection methods (multi-slit) with U. Lyon and Oncoray-Dresden Close to clinical use, few mm accuracy What about heavier beam (¹²C) ? LET grows as Z² and the nuclear interaction increase with A. Thus, for the given dose, ¹²C gives:

- less prompt γ than proton
- more background than proton

Non proton beams : something else useful? Charged fragments (protons)



BUT...

- They are forward peaked
- Energy threshold to escape the patient ~ 80-90 MeV
- They suffer multiple scattering inside the patient -> worsen the backpointing resolution

Charged secondaries have several nice features as

- The detection efficiency is almost one
- Can be easily backtracked to the emission point-> can be correlated to the beam profile & BP

MC highly unreliable, probing the very tail of the angular distribution of secondary

Secondary proton: angle vs energy

The protons could be a possible candidate for beam imaging... if they can escape the patient!! (E_{kin} >100 MeV)





The proton flux at large angle is mainly made by low energy particles.. Can be of any use for monitoring???

10

10

10

WATCH OUT!! How much are MC reliable at the moment? They are rapidly improving, but...

charged secondaries & ¹²C beam radiography



L.Piersanti et al. PMB, 2014

Secondary emission point, BP and the patient

The materials crossed to exit from the patient modifies the detected distribution (absorption & MS). Similar approach of PCT needed: exploiting the knowledge of the pencil beam transverse position and the CT deconvolute the emission shape

Measured emission shape of protons outside a 5 cm thick PMMA at 90⁰ wrt the direction of 220 AMeV ¹²C beam

L.Piersanti et al. PMB, 2014

Simulated emission distribution shape of protons as detected outside different PMMA thickness at 30^o wrt the direction of 95 AMeV ¹²C beam

'n.

Dose (a.

E. Testa et al Phys. Med. Biol. 57 4655



A non negligible production of charged particles at large angles is observed for all beam types.

> The emission shape is correlated to the beam entrance face and BP position as already measured with ¹²C at GSI. [Piersanti et al. PMB, 59 (2014)]











To be submitted to PMB

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Which detector should be used?



Integrating enough statistic (~ 10^3 events) helps to lower the accuracy on the emission point distribution (and then on the beam profile) to mm level \rightarrow detector size



- Nazionale di Adroterapia Oncologica (CNAO)
- ✓ operated in-beam
- ✓ IMMEDIATE feedback on the particle range
- \checkmark Effective both on proton and ^{12}C beam



The INSIDE PET system

- DAQ sustains annihilation and prompt photon rates during the beam irradiation
- Two planar panels each 10 cm x 20 cm wide. Each panel will be made by 2 x 4 detection modules
- Each module is composed of a pixelated LYSO scintillator matrix 16 x 16 pixels, 3x3 mm² crystals, 3.1 mm pitch, for a total sensitive area of 5x5 cm²
- One SiPM array (16x16 pixels) is coupled to each LYSO matrix.
 200 ps FWHM TOF capability





INSIDE: charged tracker

- 6 XY planes with 2 cm spacing. Each plane made of 2 stereo layers of 192 0.5x0.5 mm² square scintillating fibers
- 2x0.5 mm squared fibers read out by Hamamatsu 1mm² SiPM : S12571-050P
- 32 SiPM feed a 32 ch ASIC BASIC32





- ✓ 4x4 LYSO pixellated crystals tracking planes: 50 x 50 x 16 mm³
- ✓ Plastic absorber 1.5 cm thick in front of LYSO to screen electrons
- ✓ Crystals read out by 64 ch Hamamatsu MultiAnode



Encouraging results obtained with hydrophones at low frequency

Will modern detectors enable millimetre-accurate range verification and even tomography?

Courtesy of K. Parodi



Ionoacustic: proof of principle

Experimental setup at the MLL Tandem accelerator:

- water phantom
- 3.5 10 MHz US detector, remotely controlled
- Beam pulse width 8ns-4ms
- 10⁴ 10⁸ protons per pulse





- Lowest detectable signal of 10⁴ p per pulse -> 10¹² eV (earlier exp.: 10¹⁴ eV)
- Sub-millimeter range resolution possible
- 2D and 3D imaging capabilities
- Good agreement between simulation (Geant4 + K-Wave) and measurements

Summary & conclusions

- Particle therapy is becoming a new tool to help oncologist in the multi-approach war to cancer.
- Monitoring the beam range is a necessary step to meet the quality standard of a mature clinical technique
- The nuclear interactions of the beam provide the signal to monitor the released dose: PET- γ from β^+ emitters, prompt γ from nuclear excitation and light charged fragments from fragmentation
- Very fast R&D: solutions close to clinical practice for proton, yet on the way for ¹²C: multimodal approach
- Ionoacustic? Cheap and reliable... maybe in the future









Thanks....



CREDITS

I am in debt for a lot of slides, plots, comments, discussions and with many collegues... M.Durante, G.Battistoni, K.Parodi, D. Dauvergne & many others...

Better than proton? Maybe yes (^{12}C)

M.Kramer et al. JoP 373 (2012),



 10^{2}

LET (KeV/µm)

10⁰

10-1

10¹

ET

 10^{3}

N.B. As far as money (and the space) is the main concern.. protons win easily!

Heavier is better?



Fragmentation!

Dose release in healthy tissues with possible long term side effects, in particular in treatment of young patients → must be carefully taken into account in the Treatment Planning System

- Production of fragments with higher range vs primary ions
- Production of fragment with different direction vs primary ions

 Mitigation and attenuation of the primary beam

 Different biological effectiveness of the fragments wrt the beam



Exp. Data (points) from Haettner et al, Rad. Prot. Dos. 2006 Simulation: A. Mairani PhD Thesis, 2007, Nuovo Cimento C, 31, 2008

OER and ¹⁶O beam

The high LET of the ¹⁶O beam is effective against radio-resistant hypoxic tumors (low Oxygen Enhancement Ratio)

Bassler et al., Acta Oncol 2013





x (mm)



M.Kramer et al. JoP 373 (2012),

Full treatment or simple boost session with ¹⁶O with hypoxic can be a clear improvement with respect to conventional Radiotherapy

Charged secondary emitted from BP?

- Measurements at LNS (Catania) ¹²C beam @ 80 MeV/ nucleon. Range in PMMA phantom ~ 1 cm.
- Corresponds to the last part of the path in the patient of higher energy, longer range pencil beam -> signal from BP region
- Moving the target the charged signal follows





Agodi et al. PMB 2012

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Agodi et al. PMB 2012



Durante & Loeffler, *Nature Rev Clin Oncol* 2010

Potential advantages

High tumor dose, normal tissue sparing Effective for radioresistant tumors Effective against hypoxic tumor cells Increased lethality in the target because cells in radioresistant (S) phase are sensitized Fractionation spares normal tissue more than tumor

Reduced angiogenesis and metastatization

Courtesy M.Durante

Fragments from ¹²C beam (E_{kin}=400 AMeV) on ¹²C

The Z>2 produced fragments approximately have the same velocity of the ¹²C beam and are collimated in the forward direction

- The protons are the most abundant fragments with a wide β spectrum 0< β <0.6 and with a wide angular distribution with long tail
- The Z=2 fragment are all emitted within 20^0 of angular aperture
- The dE/dx released by the fragment spans from ~ 2 to ~ 100 m.i.p.

Do not trust MC too much!



Kinetic energy (MeV/nucl)



Secondary proton: energy distribution

Only a fraction of the p flux can exit the patient.. 80-90 MeV are needed in the worst case (deep tumor at 8-9 cm from skin)



CNAO (Pavia, Italy)

Synchrotron originally designed by TERA foundation (U. Amaldi), reingenineered, built and commissioned with the fundamental contribution of INFN; p: max 250 MeV; ¹²C: max 400 MeV/u

No. of patients at 21/05/15: 534 (405 with ¹²C)

Similar machine is being commissioned in Austria: MEDAUSTRON

New Proton Therapy in Trento (Italy)



2D imaging in one gantry room Ct on rail being installed in the second gantry room





Radiations vs Biological effects





¹²C -> good compromise between RBE and OER.

Optimal RBE profile vs penetration depth position.





Spotting structures with β⁺ activity measurement in-beam (proton beam at CNAO)



A PMMA phanton with air holes in two different positions was irradiated with protons. A uniform 2 Gy dose was delivered to a 4x4x6 cm³ PTV. The proton TP is composed of 34 energy layers with energies ranging from 62 MeV up to 116 MeV/u.

V. Rosso et al, Submitted to Nucl. Instr. & Meth.





Each profile was calculated over a volume that passes trough one air cavity. The reported profiles correspond to 360 s data acquisition and the profiles were normalized to the same area.

Typical Hype Cycle for Innovation Technology



Technology trigger

Maturity

adapted from Becker & Townsend

Helium beam @90° Charged secondaries monitoring

A non negligible production of charged particles at large angles is observed for all beam types.

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Which is the right beam for therapy?

As far as money is the main concern.. protons win easily!

If we come to effectiveness, the landscape can change.

For instance, concerning the beam selectivity, comparing lateral deflection heavier ions have less multiple scattering

