sciendo

Bio-Algorithms and Med-Systems 2022; 18(1): 96-106

Review

Karol Lang

Towards high sensitivity and high-resolution PET scanners: imaging-guided proton therapy and total body imaging

https://doi.org/10.2478/bioal-2022-0079
Received October 23, 2021; accepted December 2, 2022; published online December 19, 2022.

Abstract: Quantitative imaging (i.e., providing not just an image but also the related data) guidance in proton radiation therapy to achieve and monitor the precision of planned radiation energy deposition field *in-vivo* (a.k.a. proton range verification) is one of the most under-invested aspects of radiation cancer treatment despite that it may dramatically enhance the treatment accuracy and lower the exposure related toxicity improving the entire outcome of cancer therapy. In this article, we briefly describe the effort of the TPPT Consortium (a collaborative effort of groups from the University of Texas and Portugal) on building a time-of-flight positron-emission-tomography (PET) scanner to be used in pre-clinical studies for proton therapy at MD Anderson Proton Center in Houston. We also discuss some related ideas towards improving and expanding the use of PET detectors, including the total body imaging.

Keywords: proton therapy, imaging-guidance proton therapy, proton range verification, PET scanner, total-body PET, time-of-flight PET scanner, TOF PET, nuclear medical imaging, radiopharmaceuticals, hypoxia, cancer, theranostics, FLASH treatment, multi-modal treatment, TPPT Consortium.

***Corresponding author: Prof. Karol Lang,** Department of Physics, University of Texas at Austin, Austin, TX 78712, USA. Phone: +1 512 471 3528. Email: lang@physics.utexas.edu

Introduction: History and a bird's-eye view of proton therapy

In a seminal paper in 1946 entitled "Radiological use of fast protons" [1] Robert R. Wilson proposed proton radiation therapy (PT) as a more effective method of treating cancer compared to irradiations using electrons or gammas. He pointed out that cyclotrons would then soon reach high enough energies to penetrate an entire human body. Wilson wrote and illustrated his thesis (see Fig. 1):

"The proton proceeds through the tissue in very nearly a straight line, and the tissue is ionized at the expense of the energy of the proton until the proton is stopped. The dosage is proportional to the ionization per centimeter of path, or specific ionization, and this varies almost inversely with the energy of the proton. Thus the specific ionization or dose is many times less where the proton enters the tissue at high energy than it is in the last centimeter of the path where the ion is brought to rest.

These properties make it possible to irradiate intensely a strictly localized region within the body, with but little skin dose. It will be easy to produce well collimated narrow beams of fast protons, and since the range of the beam is easily controllable, precision exposure of well defined small volumes within the body will soon be feasible."

The first patient was treated with protons in 1954 at the Berkeley's Donner Laboratory. Soon later, accelera-

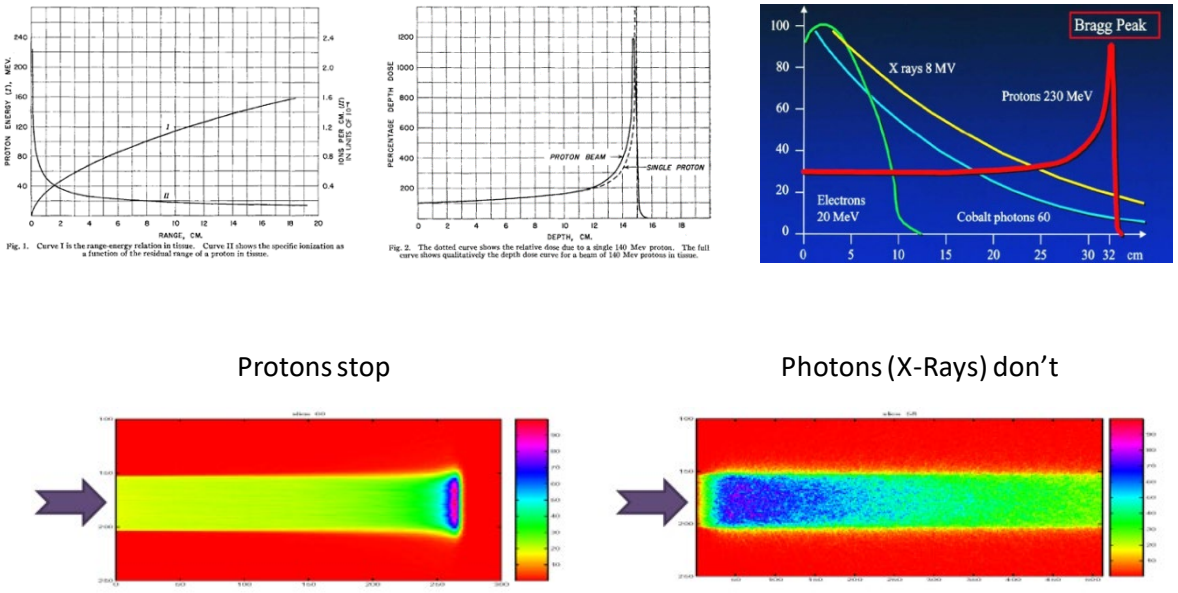

Figure 1: Wilson's figures borrowed from [1] and in color a "modern" comparison of propagation of protons and X-rays in matter. The characteristic Bragg peak for stopping protons can be used as a precision "energy knife".

-tor labs treated cancer patients with protons, e.g., Harvard Cyclotron Lab in collaboration with Massachusetts General Hospital between 1961 – 2002. The first dedicated hospital-based clinical facility started in Loma Linda in 1990. The technology followed advancements in accelerators: the first use of scanning proton beam was at the Paul Scherrer Institute in 1996, three-dimensional intensity modulated proton therapy was commissioned at MD Anderson Cancer Center in 2010. Currently, more than 100 proton treatment centers operate around the world and about as many are in various phases of construction or planning [2]. Close to 300,000 patients worldwide have now been treated using protons and other hadrons (pions and ions), about half of this number since 2014 [3]. Despite very high associated costs (recent centers cost $100-200M) the particle therapy is so compelling that it is largely considered to be the future of radiation treatment [4-6]. Overwhelming clinical evidence demonstrates that particle therapy is more effective, spares healthy organs or tissues, lowers toxicity, and increases survival of patients [7-11].

However, 76 years since the Wilson's paper, *particle therapy has not yet delivered on all its potential and promises*. This radiation treatment modality can and must be improved if its use is to dominate future radiation oncology. While the beam delivery has gone through several hardware and software transformations, and the treatment planning is now a complex and sophisticated "well-oiled" process [12], the diagnostics of efficacy of ea-

-ch irradiation treatment (a.k.a. proton range verification) has not kept up at the same pace of development despite that it could improve treatment and the assessment of its end results. Executing a radiation plan presents for each patient unique challenges that are potentially impeding the effectiveness of proton therapy. Underdose to the tumor tissue and overdose to the healthy tissue must be minimized. Problems are due to high dose gradients that are very sensitive to anatomy, its motion and change, heterogeneity in patient population, tumor characteristics, treatment techniques, or incomplete knowledge and models of relative biological effectiveness (RBE) of protons that are often based on photon therapy experience - all these factors may hinder radiation treatment. *A common denominator for mitigating all these difficulties is precise and sensitive quantitative imaging and dose monitoring of irradiation fractions*. The focus of our TPPT Consortium and the tests of its imaging diagnostics tool is a major stride commensurate with other investments and advancements in proton therapy.

Motivations for quantitative imaging-guided proton therapy

Limitations of PT

In the current era of intensity-modulated proton therapy (IMPT), the planning of conformal tissue radiation treatment receives much needed and necessary attention to details, scrutiny, and phantom verifications. Over the years, progress in medical accelerators, beam transport, as well as beam delivery systems have been assisted by advances in the software modeling of beam interactions in phantoms and patients. However, gaps in our knowledge of biological effectiveness of PT, relatively poor understanding of radiobiological effectiveness (RBE) of protons, and IMPT's significant vulnerability to anatomic, motion and other uncertainties have clouded and impeded the optimal use of PT. It is well known that RBE is a function of linear energy transfer (LET) and energy spectra at the point of interest. It also depends on the dose per fraction, tissue/cell type, and the "alpha/beta ratio" (the dose where the linear as well as the quadratic component cause the same amount of cell killing).

Interactions of protons in live tissues cause much less immune system suppression than interactions of photons, likely due to differences in the overall toxicity of the dose "bath". This difference can be maximized through IMPT optimization based on criteria that reduce the dose bath and limit the exposure of specific immune organs at risk. Reduction in immune suppression may not only improve radiotherapy outcomes but also may enhance the effectiveness of immunotherapy after radiotherapy. While IMPT is much more powerful and effective than the intensity-modulated (gamma) radiation therapy (IMRT) or the passively scattered proton therapy (PSPT), it is also more sensitive to inter- and intra-fractional position and anatomy variations and uncertainties in range or biological effectiveness. Some shortcomings like overly simplistic assumption about RBE of protons, some level of inappropriateness of extension of photon experience to protons, and non-ideal technology leave much room for improvement, despite constantly refined techniques and protocols. The bottom line is that clinical consequences of uncertainties and knowledge gaps lead to end results that push us to conclude that *the proton therapy fails to meet its expectations*.

Unmet needs of PT

While much data and simulated imaging are produced in the radiation treatment planning, not as much feedback data are generated during treatment. Monitoring of treatment is not routine and it should be stressed that CT, Cone Beam CT, MRI, or rare in-room unoptimized PET scans are sensitive to anatomical changes but are often insufficient to guide the course of treatment and fall short in evaluating each fraction or the efficacy of the therapy [13-18]. Determination of the *in-vivo* and *in-situ* efficacy of each proton irradiation remains challenging and desiring the advancement of high quality and high sensitivity imaging and dosimetry of irradiation [19-28]. A consensus is emerging that sensitive and precise in-beam *in-vivo* PET imaging may provide extremely valuable feedback that can adaptively guide the treatment and help assess irradiations results. It requires an optimized beam-scanner arrangement, a very high resolution and efficiency PET detector, and can be employed with other treatment theranostic modalities, as we propose below.

There are several modes of PT treatment plans. A conventional plan involves 25-35 fractions of about 2Gy/dose each delivered over a couple of minutes. A newer plan type uses about three 'hypofractions', each of 15-20Gy, and an emerging, perhaps still controversial yet very promising, plan is a FLASH treatment of 40-60Gy delivered in milliseconds. There are reports that FLASH radiotherapy demonstrates a better sparing effect of the healthy tissues while strongly impacting tumors. The reasons of this effect are not yet understood although the radiation-induced hypoxia and oxygen radicals are likely at play. There are inter- and intra-fraction opportunities to use PET scanners to map and measure beam activation of irradiated tissue and conduct dosimetry of possible occasional inter-fraction injections of suitable radiopharmaceuticals, including novel multifunctional sensitized Au nanoparticles. An optimized high-performance PET scanner can provide images and dosimetry data for adaptive planning that would improve an overall treatment outcome. This would be disruptive improvement and significant augmentation to current proton therapy treatment protocols.

Imaging-guided proton therapy

To demonstrate the proof-of-principle we have formed a TPPT Consortium and proposed to develop a high resolution and high efficiency in-beam PET scanner optimized for the brain or head-and-neck cancers. Brain cancer is the 10th leading cause of death for men and women in the United States (US). It is estimated that

about 24,530 adults in the US are diagnosed annually with primary cancerous tumors of the brain and that about 18,600 adults will die annually from this disease [29].

A technique that can provide precise verification of the treatment field and dose monitoring is of utmost importance to ensure effective treatment by the accurate beam delivery to the tumor. Several methods have been proposed in the literature [30-33] with the in-beam Positron Emission Tomography (PET) imaging – i.e., imaging based on back-to-back 511keV gammas resulting from electron-positron annihilations -- as opposed to in-room or offline PET. This method is identified as one of the superior approaches for proton range verification and dose assessment and monitoring. This is primarily because the in-beam PET can be employed immediately after the beam irradiation thus its imaging can be much less blurred by the washout and other physiological processes. This also enables the highest detection efficiency of measuring short-lived positron emitters (such as ^{15}O and ^{11}C) that are generated following proton activation of the targeted (tumor) area [33]. Additionally, in-beam PET imaging minimizes errors due to patient repositioning and motion due to the relatively long PET imaging session [20].

High-sensitivity brain PET scanner

The TPPT consortium

As a step towards these goals, our TPPT Consortium is pursuing an initial project – a PET scanner illustrated in Fig. 2, to be employed in a suite of tests with a proton beam, physical phantoms, and biological tissues. The TPPT PET scanner has been assembled out of 3x3x15 mm^3 LYSO crystals coupled to Hamamatsu's 8x8 SiPM's arrays with 3.2mm pitch. These photodetectors are read out by the PETSys Electronics front-end boards, featuring a custom-designed ASIC [67], and a data acquisition system so that data can be easily organized and stored on disc for further reconstruction and imaging. A basic detector element and the readout electronics are pictured in Fig. 3. Each element of the scanner was characterized in a specially designed mini-PET, shown in Fig. 4, that has an exactly the same mounting scheme as the main scanner. The preliminary energy resolution and the Coincidence Time Resolution (CTR) of a typical subset of two modules are included in Fig 4. We note an excellent preliminary

Figure 2: A schematic view of proposed PET scanner of the TPPT consortium and pictures of an actually built scanner that is currently being commissioned at the University of Texas at Austin.

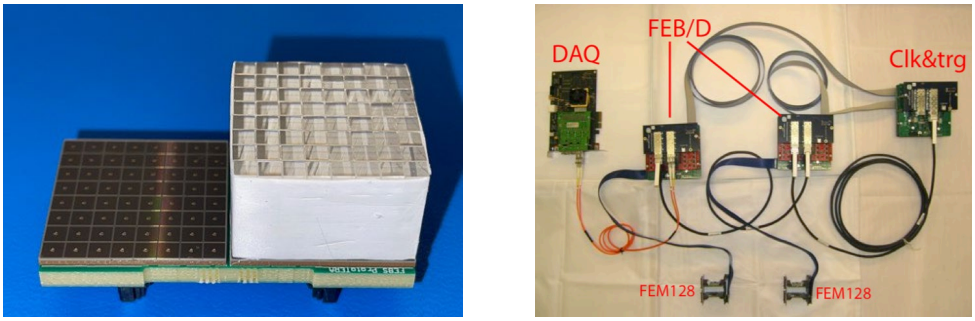

Figure 3: A basic detector element and the PETSys Electronics front-end electronics readout and data acquisition system [67].

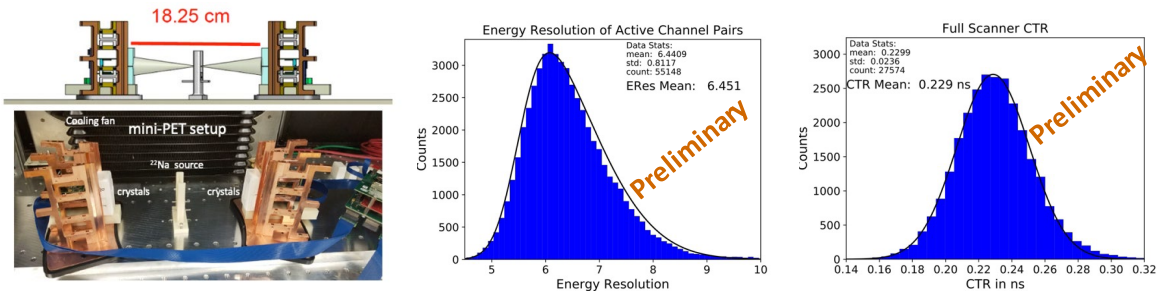

Figure 4: A schematic view and a picture of the mini-PET setup used for characterizing individual scanner modules, and the distribution of FWHM energy resolution values, showing a mean of about 6.5%, and the distribution of FWHM of CTR with a mean of about 230ps.

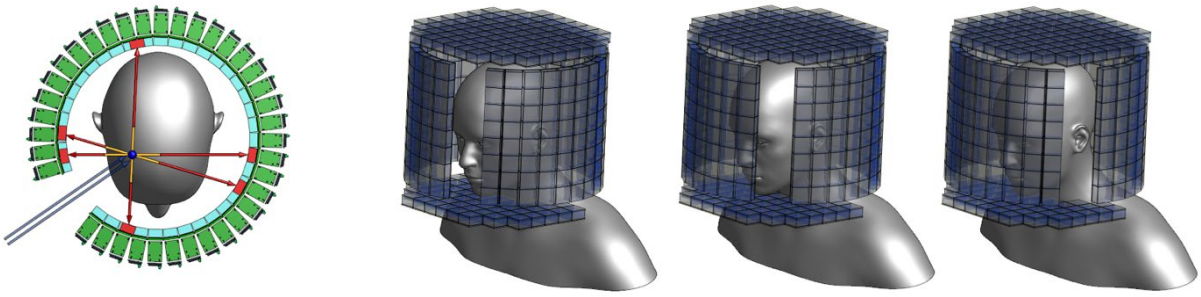

Figure 5: A schematic view and a potential realization of a brain PET scanner that features three parts: a crown and chin panels that augment the usual cylindrical section with a gap that can be rotated for the proton beam to minimize the time between the irradiation and the imaging.

performance level of 6.5% FWHM energy variance and an about 230ps FWHM CTR. Currently the scanner is being commissioned which includes optimization of SiPM over-voltages, response normalizations, and time alignment. Once the system is fully characterized it will be moved to MD Anderson for tests with the proton beam irradiating phantoms and biological tissues. We expect that the results of a suite of tests will be reported in 2023.

High sensitivity scanner

As a next step, we propose a high-sensitivity PET scanner that will have unprecedented high sensitivity and state-of-the-art timing and position resolution and will be optimized for providing feedback in proton radiation cancer therapy. The scanner could be employed immediately after the beam treatment and in between irradiation fractions to monitor the cancer tissue and inform an optimal treatment plan [20]. This work is in part a spin-off of our experience building state-of-the-art instrumentation for particle physics, and our ongoing research project at UT Austin presented above [34-36] which focuses on a small PET system being constructed for proton therapy research at MD Anderson, and from the vast experience in PET imaging and proton therapy of our MD Anderson partners.

A schematic view of the envisioned scanner is depicted in Fig. 5. The scanner will produce time-sequenced images and will serve as a feedback instrument for the proton range verification. Although our immediate focus will be the maximal impact in proton therapy, we want to point out that broader application of our scanner design is very likely. The high sensitivity and high resolution of the scanner will open possibilities for studies and diagnostics of an entire spectrum of brain functions and disorders, including traumatic brain injuries, Alzheimer's, or screening of at-risk healthy or vulnerable patients (e.g., children) for whom standard doses of radiopharmaceuticals would not be permissible [37-54]. It will be also sufficiently sensitive to exploit the positronium imaging [58-60].

Our initial simulation studies [55] indicate that the three-part scanner based on a double-ended crystal readout would provide improved energy, timing and depth of interaction resolutions thus leading to a substantial increase in sensitivity. Figure 6 partially borr-

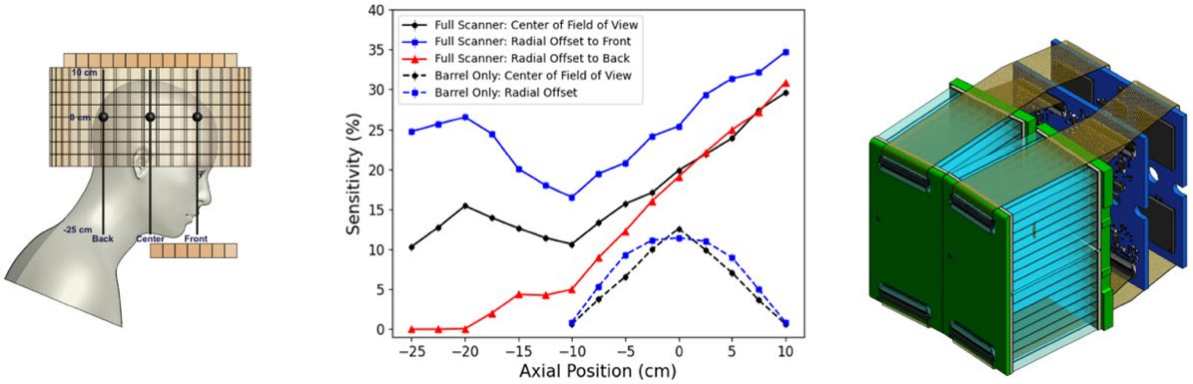

Figure 6: Left: Positions of line sources used for sensitivity predictions [55]. Middle: Absolute sensitivities for point sources placed along the line sources, for both the full scanner and barrel module alone, at the center of the radial field of view and at 10 cm radial offsets [55]. Right: Double-ended SiPM readout shown here with adapted PETSys electronics.

-ows from our earlier publication [55].

Multi-modal protocols

The majority of current in-beam PET scanners feature a design based on dual detector-head prototypes that have several drawbacks such as: a) low sensitivity that precludes the detection of the weak positron signal from the proton activated tissues, b) poor imaging performance due to the limited angle tomography, and c) typically, they use commercial PET detector modules based on previous generation technology and mechanical shields and gantry that are not optimized for the imaging conditions presented by the proton therapy that necessitates special high performance capabilities. The need for high resolution and high sensitivity scanners is further amplified when considering PET imaging of the brain where dose conformity to the tumor is essential for sparing surrounding healthy tissues.

However, the proton range verification challenge can be tackled during the fractionated treatment by employing regularly scheduled PET imaging and dosimetry that would use both the activated patient's tissues and radiopharmaceuticals as well as beam-activated pharmaceuticals based on sensitized nanoparticles. In some cases, the proton beam therapy may be combined with radioactive source treatment which could use radio-enhanced nanoparticles [56]. This could potentially soften the most critical and stringent proton range knowledge near the tumor's edge. Such multi-modal radiation treatment could be continuously monitored and adaptively revised for optimal benefits.

Total-body PET scanner and protocols

Our interests in PET scanning include also total-body scanners which are essential in the overall patient's health assessment and in for finding possible cancer's metastases. Inspired also by the J-PET successes [57-60] and hoping that it would lead to a low-cost PET scanner we have conducted preliminary studies of a scanner with 78cm diameter, shown in Fig. 7, based on plastic scintillation strips 0.62x2.54x100 cm^3 coupled to the TPPT-like readout using 8x8 SiPM's and PETSys' electronics. The present scanner exhibits high sensitivity

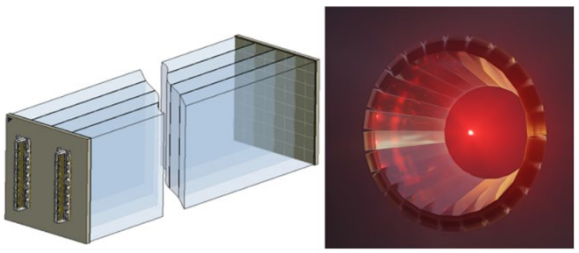

Figure 7: Preliminary design and study of a J-PET-inspired scanner.

due to its length but lacks good timing and position resolutions. In our study we have employed a simple machine learning k-Nearest Neighbor algorithm to improve imaging precision but the relatively low light

yield does not produce resolutions that would be competitive with small granularity crystals so we are now planning a study that would compare various crystals to plastics and several configuration schemes. One could imagine that high-sensitivity but limited resolution total-body scanners can be augmented with high resolution specialized inserts targeting various body areas.

Conclusions

We suggest that next advancement "frontier" in monitoring and adaptive treatment plan of proton therapy can be accomplished with optimized in-beam PET scanners and multi-modal treatment schemes. Quantitative imaging can guide therapy and improve the overall prospects of radiation cure. Clearly, this is likely to lower the patient throughput but avoids short and long-term post-radiation complications often not fully accounted for in the calculus.

A promising alternative could be the fascinating FLASH treatment [61-64] that could both provide fast therapy (more patients!) and result in lower post-radiation toxicity. PET scanners will likely play a crucial role in establishing and assessing the effectiveness of this proton radiation treatment modality. This may be a high pay-off challenge for PET scanners.

As a newcomer to the field of nuclear medical imaging and with the background in experimental particle and nuclear physics the author is compelled to express an observation that is, as it turns out, shared by many experts yet not broadly discussed. This was expressed by the author as a question posed in the context of a "Bridging Barriers" initiative - a multi-disciplinary discussion at the University of Texas at Austin:

"Can an effective collaboration be formed, modeled on research projects in experimental particle physics, that would accomplish in nuclear medical imaging what has not been accomplished over the last few decades by a number of small and isolated groups worldwide?"

Acknowledgements

We thank all members of the TPPT Consortium [34-36] supported by the UT Portugal Program at the University of Texas at Austin. The Consortium involves researchers from MD Anderson Proton Center, PETSys Electronics and C²TN in Lisbon, LIP and ICNAS in Coimbra, and the group at University of Texas at Austin group, in particular Marek Proga, Kyle Klein, Chris Layden, Will Matava, Akhil Sadam, Firas Abouzahr, John Cesar, Trang Do, Victoria Kopyleva, Shawn Park, and Tri Truong. This work has benefitted from the resources provided by the Texas Advanced Computer Center (TACC) and by the high-quality fabrication in the machine shop at the Department of Physics of the University of Texas at Austin. We acknowledge stimulating and thought-provoking discussions on the above issues with Simon Cherry, Steven Frank, Stan Majewski, Osama Mawlawi, Johan Nuyts, Katia Parodi, Joao Seco, and Stefaan Tavernier.

References

[1] Wilson RR. Radiological use of fast protons, Radiology 47, 487-491 (1946) doi:10.1148/47.5.487.

[2] An informative website on particle (a.k.a. proton or ion) therapy is maintained by a Particle Therapy Co-Operative (PTCOG) Group at https://www.ptcog.ch/index.php/.

[3] Jermann M. Particle Therapy Statistics in 2014. Int J Particle Ther. 2015;2(1):50-54.

[4] Many excellent references can be found at https://www.ptcog.ch/index.php/particletherapy literature.

[5] A website of the National Association for Proton Therapy https://www.proton-therapy.org/blog/category/press-releases/.

[6] A "white paper" of proton therapy is disseminated by a commercial enterprise PROTOM at https://info.protominternational.com/proton-therapy-white-paper

[7] Levin WP, Kooy H, Loeffler JS, DeLaney TF. Proton Beam Therapy. Br J Cancer. 93(8): 849-854 (October 2005). doi: 10.1038/sj.bjc.6602754.

[8] Lomax AJ, Bortfeld T, Goitein G, Debus J, Dykstra C et al. A treatment planning inter-comparison of proton and intensity modulated photon radiotherapy, Radiotherapy and Oncology, Volume 51, Issue 3, 1 June 1999, Pages

257-271, DOI:https://doi.org/10.1016/S0167-8140(99)00036-5.

[9] Foote RL, Stafford SL, Petersen IA, et. al. The clinical case for proton beam therapy. Radiation Oncology. 7, 174 (2012). doi: 10.1186/1748-717X-7-174.

[10] Durante M. Orecchia R & Loeffler J. Charged-particle therapy in cancer: clinical uses and future perspectives. Nat Rev Clin Oncol 14, 483-495 (2017). https://doi.org/10.1038/nrclinonc.2017.30

[11] Durante M, Debus J & Loeffler JS. Physics and biomedical challenges of cancer therapy with accelerated heavy ions. Nat Rev Phys 3, 777-790 (2021). https://doi.org/10.1038/s42254-021-00368-5

[12] Moreno AC, Frank SJ, Garden AS, Rosenthal DI, Fuller CD et al. Intensity modulated proton therapy (IMPT) - The future of IMRT for head and neck cancer. Oral Oncol.2019 Jan; 88:66-74. doi: 10.1016/j.oraloncology.2018.11.015. Epub 2018 Nov 21. PMID:30616799; PMCID: PMC6615027.

[13] MacKay RI. Image guidance for proton therapy. Clin Oncol (R Coll Radiol). 2018; 30(5):293-8.

[14] Landry G, Hua CH. Current state and future applications of radiological image guidancefor particle therapy. Med Phys. 2018; 45(11):e1086-95.

[15] Hoffmann A, Oborn B, Moteabbed M, Yan S, Bortfeld T et al. MR-guided proton therapy: a review and a preview, Radiation Oncology (2020) 15:129, https://doi.org/10.1186/s13014-020-01571-x.

[16] Zhu X, Fakhri GE. Proton Therapy Verification with PET Imaging, Theranostics 2013; 3(10):731-740. https://doi.org/10.7150/thno.5162

[17] Grogg K, Alpert NM, Zhu X, Min CH, Testa M et al. Mapping O-15 Production Rate for Proton Therapy Verification, Int J Radiation Oncol Biol Phys, Vol. 92, No. 2, pp. 453-459, 2015.

[18] Cho J, Grogg K, Min CH, Zhu X, Paganetti H et al. Feasibility study of using fall-off gradients of early and late PET scans for proton range verification, Med Phys. 2017 May ; 44(5): 1734–1746. doi:10.1002/mp.12191.

[19] Krishnamoorthy S, Teo BK, Zou W, McDonough J, Karp JS and Surti S. A Proof-of-Concept Study of an In-Situ Partial-Ring Time-of-Flight PET Scanner for Proton Beam Veri_cation, IEEE TRANSACTIONS ON RADIATION AND PLASMA MEDICAL SCIENCES, VOL. 5, NO. 5, SEPTEMBER 2021.

[20] Parodi K. Vision 20/20: Positron emission tomography in radiation therapy planning, delivery, and monitoring, Medical Physics 42, 7153 (2015); doi: 10.1118/1.4935869.

[21] Enghardt W, Crespo P, Fiedler F, Hinz R, Parodi K et al. Charged hadron tumor therapy monitoring by means of PET, Nuclear Instruments and Methods in Physics Research A 525 (2004) 284-288.

[22] Systematic analysis of biological and physical limitatios of proton beam range verification with offline PET/CT scans, Phys. Med. Biol. 54 (2009) 4477-4495; doi:10.1088/0031-9155/54/14/008.

[23] Durante M and Parodi K. Radioactive Beams in Particle Therapy: Past, Present, and Future, Front. Phys., 28 August 2020 | https://doi.org/10.3389/fphy.2020.00326.

[24] Battistoni G, Bauer J, Boehlen TT, Cerutti F, Chin MPW et al. The FLUKA Code: An Accurate Simulation Tool for Particle Therapy, Front. Oncol., 11 May 2016, https://doi.org/10.3389/fonc.2016.00116

[25] Seco J, Spadea MF. Imaging in particle therapy: State of the art and future perspective, Acta Oncologica 54 (9) 1254-1258 (2015).

[26] Shusharina N, Fullerton B, Adams JA, Sharp GC, Chan AW. Impact of aeration change and beam arrangement on the robustness of proton plans, J Appl Clin Med Phys 2019; 20:3: 14{21, DOI: 10.1002/acm2.12503.

[27] Verburg, JM, SecoJ. Proton range verification through prompt gamma-ray spectroscopy, Physics in Medicine and Biology, 59(23), 7089{7106 (2014).

[28] Seco J, Clasie B, Partridge M. Review on the characteristics of radiation detectors for dosimetry and imaging, Physics in Medicine and Biology, 59(20), R303{R347; https://doi.org/10.1088/0031-9155/59/20/R303 (2014).

[29] Statistics adapted from the American Cancer Society's publication, Cancer Facts & Figures 2021, the ACS website, the CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2013-2017, published October 2020, and the National Cancer Institute website (sources accessed January 2021).

[30] Parodi K, Enghardt W and Haberer T. 2002 In-beam PET measurements of radioactivity induced by proton beams, Phys. Med. Biol. 47 21-36.

[31] Richard MH and Chevallier M. Design guidelines for a double scattering. Compton camera for prompt-gamma imaging during ion beam therapy: a Monte Carlo simulation study, IEEE Trans. Nucl. Sci. 58 87{94 (2010).

[32] Jones KC, Nie W, Chu JCH, Turian JV, Kassaee A et al. Acoustic-based proton range verification in heterogeneous tissue: simulation studies, Phys. Med. Biol. 63 025018 (2018).

[33] Liu C, Li Z, Hu W, Xing L, Peng H. Range and dose veri_cation in proton therapy using proton-induced positron emitters and recurrent neural networks (RNNs), Phys Med Biol. 2019 Sep 4;64(17):175009. doi: 10.1088/1361-6560/ab3564.

[34] TOF-PET for Proton Therapy (TPPT) - In-beam Time-of-Flight (TOF) Positron Emission Tomography (PET) for proton radiation therapy, consortium of the University of Texas at Austin (K. Lang, PI), UT MD Anderson Cancer Center (N. Sahoo, PI), and Portugal (V. Varela, PI); https://utaustinportugal.org/projects/tppt/.

[35] TPPT Consortium: PETSys Electronics S. A. Portugal; LIP, IST (University of Lisbon), Portugal; ICNAS, University of Coimbra, Portugal; C2TN, IST (University of Lisbon) Portugal; University of Texas at Austin, Austin, USA; UT MD Anderson Proton Therapy Center, Houston, USA, Real-time in-beam Positron Emission Tomography for proton-range verification in proton radiation therapy, IEEE Symposium, 2021.

[36] Klein K, Abouzahr F, Lang K, Layden C, Matava W et al. Time-of-Flight PET for Proton Therapy (TPPT), poster at the 12th International Conference on Position Sensitive Detectors, University of Birmingham, Sep 12-17, 2021, and a poster at the 9th Conference on PET/MR and SPECT/MR and Total-Body PET Workshop, May 28-June 1, 2022, Isola d'Elba, Italy.

[37] Morbelli S, Garibotto V, Van De Giessen E, Arbizu J, Chetelat G et al. A Cochrane review on brain 18F.FDG PET in dementia: limitations and future perspectives, European Journal of Nuclear Medicine and Molecular Imaging, September 2015, Volume 42, Issue 10, pp 1487{1491.

[38] Byrnes KR, Wilson CM, Brabazon F, Von Leden R, Jurgens JS et al. FDG-PET imaging in mild traumatic brain injury: a critical review, Neuroenergetics, 09 January 2014, https://doi.org/10.3389/fnene.2013.00013.

[39] Mettler FA, Huda W, Yoshizumi TT and Mahesh M. Effective Doses in Radiology and Diagnostic Nuclear Medicine: A Catalog, Radiology 248(1), 254-263, 2008.

[40] Lewellen TK. Recent developments in PET detector technology, Phys Med Biol. 2008;53:R287{R317.

[41] Lewellen TK. The Challenge of Detector Designs for PET, AJR 2010; 195:301-309.

[42] Peng H and Levin CS. Recent Developments in PET Instrumentation, Current Pharmaceutical Biotechnology, 2010, 11, 555-571.

[43] Lee JS. Technical Advances in Current PET and Hybrid Imaging Systems, The Open Nuclear Medicine Journal, 2010, 2, 192-208.

[44] Moses WW. Fundamental limits of spatial resolution in PET, Nucl. Instrum. Meth Phys. Res. A 648(suppl): S236-S240 (2011).

[45] Vaquero JJ and Kinahan P. Positron Emission Tomography: Current Challenges and Opportunities for Technological Advances in Clinical and Preclinical Imaging Systems, Annu. Rev. Biomed. Eng. 2015 ; 17: 385{414. doi:10.1146/annurev-bioeng-071114-040723.

[46] Vandenberghe S, Mikhaylova E, D'Hoe E, Mollet P and Karp JS. Recent develop-ments in time-of-fight PET, EJNMMI Physics (2016) 3:3; DOI 10.1186/s40658-016-0138-3.

[47] Walrand S, Hesse M and Jamar F. Update on novel trends in PET/CT technology and its clinical applications,

Nuclear Medicine: Physics and Instrumentation, Special Feature Review Article, BrJRadiol 201;89:2016, 053

[48] Del Guerra A, Belcari N and Bisogni M. Positron Emission Tomography: Its 65 years, Rivista del Nuovo Cimento Vol. 39, N. 4 2016; DOI 10.1393/ncr/i2016-10122-6.

[49] Jones T and Townsend D. History and future technical innovation in positron emission tomography, J. Med. Imag. 4(1), 011013 (2017), doi: 10.1117/1.JMI.4.1.011013.

[50] Berg E and Cherry SR. Innovations in Instrumentation for Positron Emission Tomography, Semin. Nucl. Med. 2018; 48:311-331.

[51] Gonzalez AJ, Sanchez F and Benlloch JM. Organ-Dedicated Molecular Imaging Systems, IEEE Transactions on Radiation and Plasma Medical Sciences, 2(5), 388-403, 2018, https://doi.org/10.1109/trpms.2018.2846745.

[52] Catana C and Martinos AA. Development of Dedicated Brain PET Imaging Devices -- Recent Advances and Future Perspectives, Journal of Nuclear Medicine, April 26, 2019, doi:10.2967/jnumed.118.21790.

[53] Faul M and Coronado V. Epidemiology of Traumatic Brain Injury. In Handbook of Clinical Neurology, 127:3{13. Elsevier, 2015.

[54] Corso P. Incidence and Lifetime Costs of Injuries in the United States, Injury Prevention 12, no. 4 (August 1, 2006): 212{18. doi:10.1136/ip.2005.010983.

[55] Layden C, Klein K, Matava W, Sadam A, Abouzahr F et al. Design and modeling of a high resolution and high sensitivity PET brain scanner with double-ended readout, Biomed. Phys. Eng. Express 8 (2022) 025011.

[56] Kuncic Z and Lacombe S. Nanoparticle radio-enhancement: principles, progress and application to cancer treatment, Phys Med Biol 2018 Jan 9;63(2):02TR01. doi: 10.1088/1361-6560/aa99ce.

[57] Moskal P, Stępień EŁ. Prospects and Clinical Perspectives of Total-Body PET Imaging Using Plastic Scintillators PET Clin. 2020 Oct;15(4):439-452. doi:10.1016/j.cpet.2020.06.009.

[58] Moskal P, Stępień EŁ. Positronium as a biomarker of hypoxia, Bio-Algorithms and Med-Systems 2021; 17(4): 311–319.

[59] Moskal P, Dulski K, Chug N, Curceanu C, Czerwiński E, Dadgar M,et al. Positronium imaging with the novel multiphoton PET scanner. Science Advances (2021) 7:eabh4394. doi:10.1126/sciadv.abh439

[60] Moskal P, Gajos A, Mohammed M, Chhokar J, Chug N, Curceanu C, et al. Testing CPT symmetry in ortho-positronium decays with positronium annihilation tomography. Nature Communications (2021) 12:5658.

[61] Lin B, Gao F, Yang Y, Wu D, Zhang Y, Feng G, Dai T and Du X (2021), FLASH Radiotherapy: History and Future. Front. Oncol. 11:644400. doi: 10.3389/fonc.2021.644400.

[62] Spitz DR, Buettner GR, Petronek MS, St-Aubin JJ, Flynn RT et al. An integrated physico-chemical approach for explaining the differential impact of FLASH versus conventional dose rate irradiation on cancer and normal tissue responses, Radiotherapy and oncology, 2019, Vol.139, p.23-27.

[63] Maxim PG, Keall Paul, Cai J. FLASH radiotherapy: Newsflash or flash in the pan? Medical physics (Lancaster), 2019, Vol.46 (10), p.4287-4290.

[64] Liew H, Mein S, Tessonnier T, Abdollahi A, Debus J et al. The Impact of Sub-Millisecond Damage Fixation Kinetics on the In Vitro Sparing Effect at Ultra-High Dose Rate in UNIVERSE. Int. J. Mol. Sci. 2022, 23, 2954. https://doi.org/10.3390/ ijms23062954.

[65] Ros A, Barrientos L, Borja-Lloret M, Casaña JV, Muñoz E et al. New probe for the improvement of the Spatial Resolution in total-body PET (PROScRiPT), EPJ Web of Conferences 253, 09004 (2021). https://doi.org/10.1051/epjconf/202125309004

[66] Majewski S. Perspectives of brain imaging with PET systems, Bio-Algorithms and Med-Systems 2021; 17(4): 269–291. https://doi.org/10.1515/bams-2021-0178.

[67] Bugalho P, Di Francesco A, Ferramacho AL, Leong C, Niknejad T, Oliveira L, Pacher L, Rolo M, Rivetti A, Silveira M, Silva JC, Silva R, Tavernier S, Valera J, Experimental results with TOFPET2 ASIC for time-of-

flight applications, Nucl. Instrum. Meth. A 912, 195-198 (2018), doi:10.1016/j.nima.2017.11.034.