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D3.7 - Report with the review on recommended clinical and research practices in modern proton therapy

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Abstract

This report analyses the existing scientific literature, guidelines and recommendations for identifying the knowledge gaps related to medical physics and clinical issues of proton therapy. Current literature does not allow for sufficiently robust "cost/effectiveness" comparison of PT with other treatment options for a large variety of diagnoses. We highlight some of the most promising areas where further research could solidify these assumptions.

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Executive Summary

In 2018, DG for Health and Food Safety (SANTE) initiated, after the request of the European Investment Bank (EIB), a discussion on the strategy for further investment in proton therapy in Europe. The EIB was interested in receiving guidelines on the needed support for investment in proton therapy (PT). The reason for this was the growing number of financing requests for high-end proton therapy treatment centres, including an increasing number of commercial operators. The support for radiation therapy is foreseen in the program Europa's Beating Cancer and several calls within the European Association of National Metrology Institutes (EURAMET[1]) project. The needs of proton therapy in Europe are nowadays broadly discussed, also in the context of clinical and financial effectiveness as compared to conventional treatment. Therefore, the aim of this report is to analyse existing literature overviews and original publications, guidelines and recommendations and to identify gaps of knowledge related to medical physics and clinical issues of proton therapy.

International guidelines and recommendations in radiation medicine are essential for standardisation of procedures and safety of patients. In the last two decades the International Atomic Energy Agency (IAEA[2]), the International Committee of Radiation Units and Measurements (ICRU[3]), the American Association of Medical Physicists (AAPM[4]) and the Proton Therapy Co-Operative Group (PTCOG[5]) published several reports, guidelines and recommendations, which are now applied by PT community. The standardisation of reference dosimetry for scattered proton beams is based on the IAEA report TRS-398 (Andreo P et al. 2000) and the report update for Pencil Scanning Beams is the process of publication. Medical Physics recommendations for PT with scattered beams were published by ICRU in 2007 (ICRU 2007). Recently, a new Report Committee has been approved and the updated report, which takes into account the recent progress in technology, is expected by 2026. In the previous years, the AAPM has published several reports on PT, such as the TG-224 on comprehensive machine quality assurance (Arjomandy et al. 2019), TG-256 on the relative biological effectiveness of proton beams in radiation therapy (Paganetti et al. 2019) and the TG-290 on respiratory motion management for PT (Li et al. 2022). A new report, the TG-359 on FLASH radiation dosimetry, is under preparation. These reports present the most recent, comprehensive recommendations and take into account the impact on the new technologies, including Pencil Beam Scanning. The European Particle Therapy Network (EPTN[6]) and the PTCOG play a growing role in the landscape of international organisations. The activities of PTCOG are channelled in 16 specific subcommittees. The yearly PTCOG conferences, gathering more than 1000 registered participants, are considered as the most important events in the PT world. EPTN was established in 2015, as a response for the need of cooperation by the growing number of proton therapy centres in Europe, and in 2017, it became a task force of the European Society Radiation Oncology (ESTRO[7]). The EPTN activities are channelled in seven working groups dealing with Clinical, Dose Assessment and Quality Assurance, Education, Image guidance, treatment

[1] EURAMET: European Association of National Metrology Institutes
[2] IAEA: International Atomic Energy Agency
[3] ICRU: International Committee of Radiation Units and Measurements
[4] AAPM: American Association of Medical Physicists
[5] PTCOG: Proton Therapy Co-Operative Group
[6] EPTN: European Particle Network
[7] ESTRO: European Society Radiation Oncology

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planning systems (TPS), Radiobiology and Health Economy. One of the EPTN aims is to provide Europe with prospective data registration programs for the most common tumour types treated with particle therapy. The collaborative approach has a good chance to harmonise the patient treatment in Europe and to deliver valuable data for evidence based medicine.

Modern PT treatment units with scanning beams offer a substantial advantage over the conventional photon therapy due to significant reductions in normal tissue doses. It may bring further health benefits not only by improvement of survival but also in the long term for reducing number of complications, improving quality of life and decreasing the probability of secondary cancers for long surviving children and young adults. Therefore, there is an acute need to consolidate clinical research to show in which cases proton therapy demonstrates clinical advantages over conventional techniques. However, validating and implementing new radiotherapy techniques have always been difficult and almost exclusively based on superiority of dose distribution and the safety of the treatment. This is because new technologies in radiotherapy are usually introduced faster than the results of clinical studies using the former technology become available. Considering the economic pressure that health care systems are facing, a demonstration that higher-cost PT is more effective – or that the methodical superiority might justify higher costs in some patient-safety-oriented way – is urgently needed.

The classical approach is based on randomised controlled trials but this methodology in some cases has been proven ineffective. Conduction of **randomized controlled studies in PT** undoubtedly requires an international network e.g. as proposed by EPTN and PTCOG. For tumours with low incidence, prospective data collection in international databases should be encouraged. As an example, ESTRO and the European Organization for Research and Treatment of Cancer (EORTC[8]) have developed a database platform and an associated research protocol (EORTC-ESTRO 2022) that will accrue patients with sarcoma, central nervous system (CNS), head and neck, breast, lung, oesophageal or prostate cancers in an open-ended prospective non-interventional non-therapeutic cohort study. In addition to pivotal randomized controlled trials (RCT), intended to demonstrate and confirm the safety and efficacy of a treatment, EPTN has proposed alternative evidence based methodologies e.g. model-based selection for normal tissue complication probability (NTCP) based clinical trials. EPTN has proposed to create a prospective data registration programme for all patients treated in European particle therapy centres. Prospective data registration provides major opportunities to continuously improve the quality of particle therapy, by defining benchmarks, to identify best practices that may help others to improve quality of particle therapy, to synchronize selection criteria and to create more homogeneous patient cohorts to evaluate results, which is particularly important in rare tumours.

Reducing the cost barrier and improving the effectiveness of treatment are possible through both technical developments of the accelerators, improvements in its application such as image guidance and combination with further innovative techniques. Progress in this field will make the treatment possible for a broader group of patients. The report summarises several recent review publications, which are paving the way of future progress in this area. (i) In **proton accelerators**, significant decrease of costs has been obtained by introduction of synchrocyclotron with superconducting magnets. Further improvement could be obtained by developing superconductors with higher critical current,

[8] EORT: European Organization for Research and Treatment of Cancer

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which would allow a higher magnetic field. Many efforts are directed towards laser driven proton accelerators but the performance of these systems is still far from clinical needs. (ii) First clinical results obtained with a high-dose-rate of electron beams **(FLASH therapy)** for shallow skin tumours are reported and stimulated corresponding research in PT. Cyclotrons and laser –driven systems are able to deliver the required beam intensities. In a roadmap to FLASH clinical trials [Taylor 2022] the key questions were defined for reproducibility of the treatment concerning parameters of the treatment plan, biological response to FLASH treatment, the possibility to apply FLASH to deep-seated tumours and to introduction of FLASH into the overall care matrix of a patient. (iii) One of the main needs in PT is **a reduction of range uncertainties**. Several techniques were developed based on single- or dual-energy computed tomography (CT), photon counting, proton CT, MRI based predictions, range probes and prompt gamma rays but no one of these techniques demonstrated clinical superiority. (iv) **Image guidance and the corresponding motion management** is an unsolved problem in PT. In the available literature, guidelines and roadmaps for IGPT are missing how to realize the catch-up of IGRT in particle therapy. An on-line adapted workflow for PT remains an open research question, which makes the realization of the time resolved treatments for moving targets unrealistic. Also some major research investments are needed to catch up with photon therapy, when it comes down to implementing online MR-guided particle therapy systems. (v) **Biological optimization of PT and the clinical value of RBE** is currently a hot topic. The AAPM Report 256 (Paganetti et al. 2019) concluded that the current clinical practice of using a constant RBE for protons should generally be maintained but in specific clinical situations could be reconsidered. Better understanding of this issue should be brought by dedicated biological research, including *in vitro* mechanistic and novel cell experiments, studies on cancer cells and normal cells exposed to protons, multicentre data-banking from proton versus photons and multicentre bio-banking to understand the biological and long-term effects of proton. (vi) **In dosimetry of Pencil Scanning Beam** the new IAEA Code of Practice will be published 2022/2023, which helps in unification of the current dosimetric practices. There are no primary standards for proton beams and the corresponding dosimetry in Europe. In addition, the establishment of the machine-specific reference fields for the transfer of the dosimetry standards will improve the status of clinical dosimetry. (vii) **Out of field doses and the risk of secondary cancer** is a subject of an active scientific debate, in particular in treatment of children and young adults. Despite a long discussion, there is still no consensus on how to support decision making in avoiding non-essential radiation risks.

Despite many technical, financial and organizational difficulties, the perspectives of further development of proton therapy are promising. The main barrier for the further growth of proton therapy remains the high price of the investment and operation and incomplete evidence of superiority from the patient perspective for more tumours and situations. More research is needed to reduce the equipment price and to achieve technical capabilities equivalent to those available in classical radiotherapy in terms e.g. of image guidance. Progress in this field is needed not only to decrease the costs but also to improve the efficacy and to make the treatment possible for a broader group of patients. The most urgent need is to consolidate clinical research to show in which cases proton therapy demonstrates clinical advantages over conventional techniques. To do so, European efforts to increase PT capacity should be coordinated and integrated in European-wide clinical studies, following homogenised rules for data exchange and quality control.

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1. Introduction

The fast technological advances of proton therapy (PT) in the last decade, enabling the use of rotating gantries, beam delivery with fast pencil-beam scanning, image-guided particle therapy and intensity-modulated particle therapy lead to a significant increase in the number of clinical centres and patients treated worldwide. A range of solid tumour sites is now treated with a clear theoretical benefit for improved tumour control and reducing side effects. In the last decade, a significant number of scientific papers and reports were published in the field of PT. Despite the fact that several guidelines and recommendations became recently available, they are not fully conclusive for researchers and policy makers.

In 2018, DG for Health and Food Safety (SANTE) initiated, after the request of the European Investment Bank (EIB), a discussion on the strategy for further investment in proton therapy in Europe. EIB was interested in receiving guidelines on the needed support for investment in PT. The reason for this was the growing number of financing requests for high-end PT treatment centres, including an increasing number of commercial operators. It was realized that PT requires considerable resources: intensive investments, expensive equipment, infrastructure and highly specialized personnel. In addition, geographical coverage of PT centres was non-uniform; as small countries had too few patients to justify their own centres but the access for patients from other countries (regions) was limited. The aim is to support the EIB in developing a better understanding of the needs for proton therapy treatment and centres in Europe.

Therefore, a Subgroup on PT Centres was created in the Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases. The group was established with participants from Member States, the European Commission, European Particle Therapy Network (EPTN) and the EIB to address key questions for future funding decisions. The mandate of the sub-group was to examine the current state of play of availability and use of proton therapy centres across the European Union (EU) and to identify options through which willing member states can cooperate sustainably to improve information exchange and avoid duplication of effort. The group underlined the need for the improved study design, improved metrology, closer networking between centres and improved patient registries and databases, to increase the knowledge and evidence bases. The consensus also applied to the need of:

i) supporting research;

ii) promoting collaboration between centres; and

iii) using conditionality in investment support.

The sub-group postulated to put on hold investments in PT until the need for/benefit of proton therapy is confirmed. Despite that, the number of PT centres in Europe is growing fast. According to the yearly updated PTCOG web page at the end of 2021, 28 proton therapy centres were present in 13 European countries. In Austria, Belgium, Czech Republic, Denmark, Poland, Sweden, Switzerland single PTC were in operation, two in Spain, three in France, Italy and The Netherlands, five in Germany and the United Kingdom. In Norway, the construction of PTCs in Oslo and Bergen were advanced. In October 2021, the Amancio Ortega Foundation agreed to donate 280 million euros to buy ten proton accelerator machines to treat cancer that will be located across Spain in different autonomous regions. However,

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in recent years the commercial Rinecker Centre in Munich and Rutherford Cancer Centres in the UK went into liquidation.

The EU has already funded a number of open projects and calls, in which PT is partially or the main object of investigation (see Appendix 1). The support for radiation therapy is also foreseen in the program Europa's Beating Cancer and several calls within the European Association of National Metrology Institutes (EURAMET) project. Within the report existing literature overviews and original publications, guidelines and recommendations are reviewed in order to identify gaps of knowledge related to radiation protection, dosimetry, radiobiology and related medical physics issues of proton therapy.

The ultimate goal of this report is to propose the collaborative approach on the European level to verify the clinical data, which are spread out and still limited. This report will be of particular interest for the newly developed PT centres in planning their research and upgrading the clinical practice to fully exploit the opportunities provided by this promising technology. By doing so we address a concrete question of DG Health put to the PIANOFORTE partnership during the proposal process on how guidelines can contribute to improve the research and clinical practice in PT.

The report consists of three parts:

(i) review of recommendations issued by major international organizations, such as the International Commission on Radiation Units and Measurements (ICRU), International Atomic Energy Agency (IAEA) and American Association of Medical Physicists (AAPM), Proton Therapy Cooperative Group (PTCOG) and European Particle Therapy Network (EPTN);

(ii) review of present clinical situation and the proposed approach to improve evidence and harmonizing practices to deliver valuable data for evidence-based medicine;

(iii) review of research needs in the field of technology and medical physics, which may improve the quality and outcome of treatment.

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2. Recommendations of international organizations – status and the need for update

In the last fifteen years, there has been a large expansion in proton therapy worldwide. Currently, the number of centres is almost fourfold larger and beam delivery, treatment planning and quality assurance (QA) technologies have significantly advanced. However, clinical recommendations and guidelines might partly not reflect this reality.

The International Commission on Radiation Units and Measurements (ICRU) **Report 78** "Prescribing, Recording, and Reporting Proton-Beam Therapy" (ICRU 2007) has not been updated yet. It provides recommendations on radiation biology, beam delivery, dosimetry, dose-volume definitions, treatment planning, motion management, uncertainty, quality assurance and prescribing, recording, and reporting treatment. Along with the expansion of treatment facilities, there has also been immense development in technology, procedures and clinical experience that altogether call for new guidelines for prescribing, recording, and reporting proton therapy.

Pencil Beam Scanning (PBS) has now become the predominant delivery modality, with all new and planned facilities being almost exclusively PBS based. The adoption of PBS as the state-of-the-art modality significantly affects all aspects of proton therapy and therefore questions the relevance of ICRU Report 78 (ICRU 2007). PBS involves the placement and delivery of many individual beams distributed throughout the tumour and allows for great flexibility in its application. However, it is particularly challenging to ensure safe and deliverable treatments. PBS also has a complex temporal dynamic, which needs to be considered in plan and machine QA. This aspect is particularly intricate when treating tumours in movement-prone sites.

Although the ICRU Report 78 (ICRU 2007) states that "the biological effects of proton beams have no known or predicted advantages", there is an increasing body of evidence showing a differential response on DNA damage response, cell cycle distribution, cell death and radio-resistance compared to photon therapy (Vanderwaeren et al. 2021). The relationship between relative biological effectiveness (RBE), defined as "the ratio of the photon dose to the proton dose required to give the same biological effect under identical irradiation conditions", and linear energy transfer (LET) is described with an increase in both quantities at the end of the proton range. A generic, tissue independent average RBE value of 1.1 is recommended as "no clinical experience has been reported indicating an RBE different from 1.1" and "no proton RBE determinations [exist] for human tissues" (ICRU 2007), though. This recommendation is supported by the literature (Paganetti and Giantsoudi 2018) due to the absence of robust models and evidence in favour of variable RBE models. Recent studies, however, have correlated toxicity with increased RBE at the distal-edge (Eulitz et al. 2019; Bahn et al. 2020; Peeler et al. 2016; Bauer et al. 2021; Underwood et al. 2018) and have investigated human tissues (Paganetti 2014). Although more reproducible studies, considering patient variability and outcome follow-up, are still required, the standardization of calculation and reporting of LET and RBE-weighted doses is already necessary.

Prevalent beam delivery technology and dosimetry guidelines have also progressed. The field has gradually moved towards PBS systems that employ energy layers, use dynamic apertures and allow for intensity modulation. New manufacturers with unique systems, e.g., Mevion, have become more

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prominent and new delivery techniques are becoming clinical, i.e., ultra-high dose rate (UHDR) or FLASH, arc therapy and spatial fractionation. However, recommendations and guidelines for novel strategies are still insufficient and non-harmonized. Therefore, in 2022 a new ICRU Report Committee started to work on the new proton therapy report. The new report is planned to review the current PT technology, including accelerators, gantries and their design, beam delivery techniques, proton specific immobilization, image guidance and motion management. Separate chapters will deal with dosimetry for PT, biology, treatment planning, uncertainty, robustness and clinical applications.

One of the main tasks of the *International Atomic Energy Agency (IAEA)* in the field of dosimetry in radiotherapy is development of the Code of Practice (CoP) for dosimetry of external beams in radiotherapy. The CoP as the **Technical Reports Series 398** "Absorbed Dose Determination in External Beam Radiotherapy" (Andreo P et al. 2000) was published in 2000 and later updated in 2005. This CoP based on standards of absorbed dose to water has been developed for the dosimetry of radiotherapy beams when ionization chambers calibrated using these standards are available. One of the chapters of the TRS-398 (Andreo P et al. 2000) is devoted to dosimetry of passively scattered proton beams but the development of the PBS technology made this part of the report incomplete.

For dosimetry, to date, there is no primary standards dosimetry laboratory providing direct reference calibrations for proton beams. However, significant effort has been made to develop primary standard level calorimetry (water and graphite) (Renaud et al. 2020). Quality correction factors are based on chamber calibrations in ^{60}Co beams as reference and on analytical calculations (Medin, Andreo, and Palmans 2022). Therefore, the updated version of TRS-398 (Andreo P et al. 2000) has been prepared and is under consultation. It includes broad scattered, uniformly scanned, and PBS intensity modulated beams, chamber recombination corrections for continuous and pulsed beams and it considers the recommendations for mean excitation energies, graphite density and analytically re-calculated beam quality factor (kQ) values from the ICRU Report 90 (ICRU 2016). For protons, there are also recommendations on reference measurement depths for broad and pencil beams, limits of use of cylindrical chambers, monitor calibration by dose-area product methodology and the recalculation of stopping power ratios.

As PBS systems became prevalent, treatment planning became increasingly based on mathematical optimization. The planning target volume (PTV) concept, which assumes that the clinical target volume (CTV) receives the prescribed dose as it moves within the PTV, may be disrupted as range and setup uncertainties lead to dose and tissue heterogeneity misalignment, affecting CTV coverage. With advances in treatment planning systems (TPS), range uncertainties can be mitigated using intensity modulation, robust optimization (RO, and evaluation, RE), which favours CTV-based strategies (without PTV) (Hernandez et al. 2020). However, increased dose sculpting may also raise treatment complexity and, at the same time, highly conformal plans may decrease robustness towards treatment errors and may lead to insufficient target coverage or even toxicity. Currently, methodologies for plan complexity and robustness control and evaluation are very heterogeneous (Kaplan et al. 2022). Given their potential and increasing availability in TPS, recommendations concerning appropriate methods and metrics need to be defined and harmonized. Furthermore, LET- or RBE-based treatment optimization and treatment planning for novel techniques, e.g., FLASH, may already be available but also lack guidelines and consensus for clinical implementation.

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Motion management seeks to mitigate the effects caused by anatomical changes, respiration, cardiac motion and peristalsis, with passive and active strategies based on imaging and treatment planning techniques. Besides traditional approaches, e.g., beam margins, beam orientation selection robust to motion, voluntary and active breath-hold techniques, modern treatment planning includes spot size expansion, spot spacing reduction, scanning and delivery pattern modification, dose repainting, 4D RO and RE, which consider setup errors, respiratory motion and the interplay effects between anatomical motion and delivery sequence. It is also common in clinical practice to use the overlay of CTV position boundaries collected during 4DCT, called the internal target volume (ITV), in combination with other strategies to account for residual motion uncertainties, i.e., breath-hold, compression belts and density overrides. Techniques further implemented for PT include CBCT for online adaptive planning, use of CT-on-rails, fluoroscopy with implanted markers and surface guidance. In recent years, there has been an upsurge in surface tracking technology, in which the patient's surface motion is used as a surrogate to infer the position and movement of the internal target. It can be combined with respiratory gating to control the treatment beam, i.e. delivery only happens when the patient is in a specific phase of their respiratory cycle (Pakela et al. 2022). While there is a wide variation in available strategies, there is still a lack of clinical standardization (Freislederer et al. 2022).

For the assessment of planning techniques and the development procedures, *the American Association of Physicists in Medicine AAPM* **Task Group Report 290**: Respiratory motion management for particle therapy (Li et al. 2022) recommends longitudinal 4DCT evaluations, multiple breath-hold scans (or *in silico* deformable techniques). Procedures should be site-specific and describe: patient immobilization, imaging, criteria, e.g., breath hold, phase gating, beam arrangement, CT number or stopping power overrides, optimization parameters and image guidance.

Sources of uncertainty are inevitable and identified in the clinical, biological and physical realms: from the diagnosis, tumour extent, radiation sensitivity, intra- and inter-fraction changes, residual range, to dose calculations and machine delivery. The developments to tackle these uncertainties were multiple in the last decades: improved imaging, e.g. functional, real-time, on-board, 4D, dual-energy, photon counting and proton CT, biomarkers, artificial intelligence (AI), e.g., automatic contouring, planning, adaption, motion management, e.g. gating, breath-hold, re-scanning, in vivo range verification, GPU accelerated Monte Carlo and probabilistic planning, with comprehensive RO and RE. Many recommendations remain, i.e. uncertainty analysis, minimization and documentation, but standardization and further recommendations are still necessary.

For QA, the **AAPM task group 224:** Comprehensive proton therapy machine quality from 2019 (Arjomandy et al. 2019) comprehensively describes the QA procedures (beam delivery mechanisms, beam parameters, and instrumentation) applicable to any generic proton radiotherapy machine, and recommends tolerances for parameters that directly influence the accuracy and precision of beam delivery. It is based on the ICRU recommendations for delivered dose to a target volume in the patient within –5% and +7% of the prescribed dose. The frequency of various tests are determined by risk assessment analysis. The report comprises double scattering, PBS and uniform scanning techniques and recommends different daily, weekly, monthly and annual tests for dosimetry, patient setup verification, mechanical parameters, imaging and safety. It also highlights the importance of independent audits.

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The AAPM **TG-256** on the Relative Biological Effectiveness of proton beams in radiation therapy published their report in 2019 (Paganetti et al. 2019). This Task group report outlined the basic concepts of RBE as well as their biophysical interpretations and mathematical formulations. The group concluded that the current clinical practice of using a constant RBE for protons should generally be maintained but in specific clinical situations could be reconsidered. For that, there is a need to identify sites and treatment strategies where variable RBE might be safely utilized. The report underlined the need for collecting clinical data of RBE doses and their correlation with clinical outcome. It was postulated to assess the potential clinical consequences of delivering biologically weighted doses based on dose-averaged LET (LET_d) and/or RBE and as a function of dose and biological endpoints. The need to assess the potential for harm and benefits associated with the clinical implementation of variable RBE and LET models into TPS was underlined. Finally, the group asked for more experimental work to understand the relationships among *in vitro*, *in vivo*, and clinical RBE and to develop recommendations to minimize the effects of uncertainties associated with proton RBE for well-defined tumour types and critical structures.

The newly appointed AAPM **Task Group No. 359** is preparing a report on FLASH radiation dosimetry, including proton FLASH. The aim of report is to standardize dosimetry for FLASH beams used in experiments, research and in preclinical applications, to assess the beam dosimetric characteristics in FLASH mode, the suitability of radiation measurement equipment (ion chambers, film, diodes, Faraday cup, etc.) and to provide general guidelines on calibration, dosimetry and reporting of beams in FLASH mode.

The Particle Therapy Co-Operative Group (PTCOG), founded in 1985, is a non-profit worldwide organization of scientists and professionals interested in proton, light ion and heavy charged particle radiotherapy. The mission of PTCOG is to promote science, technology and practical clinical application of particle therapy, with the ultimate goal of improving treatment of cancer to the highest possible standards in radiation therapy. The activities of PTCOG are channelled in 16 specific subcommittees, which work to exchange knowledge and experience in specific scientific and technical fields of particle therapy. Every year PTCOG organizes a conference, which gathers more than 1000 registered participants. PTCOG issued two reports: Shielding Design and Radiation Safety of Charged Particle Therapy Facilities (Ipe et al. 2010) and the PTCOG Safety Group Report on Aspects of Safety in Particle Therapy (Flanz et al. 2016).

The European Particle Therapy Network (EPTN) was established in 2015 as a reaction to the growing number of proton therapy centres in Europe treating the patients with PBS technology. In addition, the need to cooperate among centres and integrate particles (i.e. protons and carbons) in the framework of clinical research networks was identified as being of paramount importance. ESTRO, at the time of initiation of the network, was asked to collaborate with EPTN and agreed to facilitate the group. In 2017, EPTN became a task force of ESTRO. The EPTN activities are channelled in seven working groups on different aspects: Clinical, Dose Assessment and Quality Assurance, Education, Image guidance, TPS, Radiobiology and Health Economy.

The aim of EPTN is to promote and foster clinical/translational research collaborations, as well as education, between the European particle centres, to integrate this radiation modality in the overall radiotherapy community in Europe. Ideally, all European PT centres would collaborate in EPTN and the activities would be well aligned with general developments in cancer research and patient care. Key is

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to avoid any divide between health particle and photon radiotherapy professionals. In 2017, EPTN associated its clinical research, where appropriate, with EORTC, which has the regulatory expertise and conducts research under conditions of resolute independence and accountability. It is the firm hope of the authors that collaboration with such a non-profit cancer research organization may substantially foster the research endeavour for PT in Europe and may optimize patient's accrual when compared to single centre and/or national research initiatives only. One of the aims of EPTN is to provide Europe with prospective data registration programs for the most common tumour types treated with particle therapy. To this end, the common research platform E2-RADIatE (EORTC-ESTRO 2022) will pioneer an open-ended prospective non-interventional non-therapeutic cohort study (PARTICLECare, EORTC-1833). The cancer patient data will be prospectively captured for CNS, head and neck, or breast tumours, sarcoma, lung, oesophageal and prostate cancer. It is foreseen that the first patient will be included in the EORTC-1833 by the end of 2022.

In the PT community the current landscape and the division of work of international organizations is relatively well established. An update of the Code of Practice for dosimetry of external beams in radiotherapy (Andreo P et al. 2000) is expected to be published soon. ICRU appointed the new Report Committee to prepare the updated publication (ICRU 2007) on prescribing, recording, and reporting Proton-Beam Therapy. AAPM remains very active providing high-quality reports published in peer-reviewed journals. The newly appointed AAPM Task Group No. 359 is working to prepare a report on FLASH (ultra-high dose rate) radiation dosimetry, including proton FLASH. PTCOG works in 16 subcommittees and organizes yearly, very well attended world conferences on particle therapy. In Europe EPTN appointed seven working groups to foster collaboration between 23 proton therapy centres. Collaboration between the European particle centres will support clinical research, harmonisation of patient treatment and deliver valuable data for evidence based medicine.

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3. The need for collaborative clinical trials in proton therapy

3.1 Introduction

PT is currently a divisive issue on the worldwide healthcare scene as to whether the potential clinical benefits are worth the extra cost. Detractors might consider that the gap in favour of PT for the so-called “consolidated” indications has shrunk in the last three decades due to advances on photon-based techniques, computer science, accelerator technology, imaging, intensity modulation and stereotactic techniques (Thariat et al. 2013). The latter techniques can produce steep gradients using photon fluence modulation and multiple mini-beams to partially compensate for the intrinsically sub-optimal photon dose distribution. The dose can also be delivered to moving tumours, using sophisticated in-room image guidance. Yet, the advantages of PT compared to photons in terms of low dose spread in children and young adults are widely admitted with respect to the risk of second cancer risks.

Moreover, recent major PT advances, with miniaturization of proton accelerators, implementation of active scanning and development of in-room imaging, have substantially modified the landscape, costs, and clinical potential of PT. PT centres can now be situated within health care centres and the number of PT facilities continues to dramatically increase worldwide (Weber et al. 2017; Hrbacek et al. 2016). With such technical improvements and generalization, PT is reaching its maturity and can intend to contribute to evidence-based medicine. A plethora of potential new indications for PT can be proposed to decrease the morbidity, sequelae (and associated societal costs), and risk of second cancers, and to escalate the dose in tumours unsatisfactorily treated with photons (Jakobi et al. 2015).

Implementing new radiotherapy techniques has always been difficult. Considerable financial and political pressure has always been put on radiation oncologists to improve their performances and quality of care. In contrast, little means have been given to radiotherapy although it is a very cost-effective anti-cancer treatment, compared to some systemic therapies, which create a tremendous buzz for a modest benefit in less than 15% of patients, at an extremely high cost and in absence of true predictive biomarker for patient selection. Intensity modulated Radiotherapy (IMRT) was validated through a small phase-3 trial in 2011 (Nutting et al. 2011) after years of implementation in routine practice in some countries. It is now massively implemented to the point where 3D radiotherapy is no longer considered ethical. The SBRT paradigm shift for oligometastases was reported in 1995. Yet, first evidence was only recently reported in two randomized phase 2 trials, at a time where SBRT is massively used in routine practice (Palma et al. 2019). SBRT is delivered using dedicated or versatile SBRT machines and patients who benefit from it are numerous.

The development of clinical research to improve the level of evidence of PT is being given full consideration and several international groups actively contribute to investigating and providing evidence for PT. In view of the higher investment cost of PT (which should decrease in the coming years) and the lack of proper reimbursement of PT, building evidence for PT through high quality data is an urgent necessity.

Numerous guidelines have been established since 2010 by international groups (PTCOG and EPTN among others) and they provide clear directions for the enlarging community of PT users. These

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guidelines cover many issues including radiobiology, physics, image guidance, delineation rules, proton treatment planning and delivery, and clinical trials (Hrbacek et al. 2016; Stock et al. 2019; Bolsi et al. 2018; Chang et al. 2017; Crouzen et al. 2022; De Roeck et al. 2022; Lin et al. 2021; Patel et al. 2022; Weber et al. 2020).

3.2 Randomized controlled trials (RCT)

PT has dose distribution advantages, but demonstration of a clinical benefit calls for randomized controlled trials. The main reasons to perform randomized control trials is to ensure that all factors (known or unknown) potentially influencing response to radiotherapy, are well balanced between groups of patients allocated to either form of radiotherapy (photons or protons). Effective conduction of large randomized controlled studies in PT requires international collaboration, such as proposed by the EPTN (Weber et al. 2020). Within cooperation, the Health Economy work package considers the different organization of health care and different financing/reimbursement systems. The Clinical work package aims at creating a basis for evidence-based particle therapy at a European level.

EPTN has promoted more than 10 large, potentially practice-changing randomized trials. In clinical trials, patient enrichment (to optimize the ratio and cost of patients' accrual over patients' benefit) may, when indicated, be performed before randomization based on a normal tissue complication probability modelling (NTCP) (Tambas et al. 2020; Langendijk et al. 2013). In this framework, endpoints of PT randomized trials can be on toxicities using validated scales for early and late toxicities. They can also include Patient-Reported Outcome Measures (PROM) and quality of life endpoints (Meadows 2011). In addition to randomized trials, EPTN has established alternative evidence-based methodologies such as model based selection, uniform prospective data registration using a data collection infrastructure (with support by EORTC).

3.3 Prospective data registry

In clinical situations where there are no randomized trials available or such trials are not possible, prospective data collection in national or international databases should be encouraged (Weber et al. 2020). PT is considered as an excellent treatment option for children and young adults with cancerous and non-cancerous tumours. In the US, the Paediatric Proton Consortium Registry (PPCR) was established to expedite proton outcomes research in the paediatric population requiring radiotherapy in 2010 and the first patients were enrolled there in 2012. The registry collects demographic and clinical data, which PT centres collect in their routine operation. It is likely and much desired that EPTN would join this initiative (Weber et al. 2019).

This may typically occur for tumours with low incidence or tumours from patients not eligible for randomized trial for various reasons, such as previous history of cancer, severe comorbidity, or patient refusal. The previously mentioned ESTRO-EORTC database platform and associated research protocol, the E2-RADIatE (EORTC-ESTRO 2022), will accrue patients with different tumours in open-ended prospective non-interventional non-therapeutic cohort studies. This database includes the recording of generic information, e.g., tumour site, tumour type, stage, previous cancer treatment, as well as specific data, e.g., radiation dose, acute and late toxicity, outcome data, and possible dosimetric data

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for various tumours. Data transfer tests are being performed now in few European PT centres, and an agreement form to be signed by all participating institutions is being finalized.

Doing so, the EPTN will be able to address differences between European PT centres on criteria for patient selection, resulting in major heterogeneity of patient populations and eventual outcome, and to propose harmonization strategies. Prospective data registration provides major opportunities to continuously improve the quality of particle therapy, by defining benchmarks, to identify best practices that may help others to improve quality of particle therapy, to synchronize selection criteria and to create more homogeneous patient cohorts to evaluate results, which is particularly important in rare tumours (Stock et al. 2019).

3.4 Future directions

PT has reached a level of technical sophistication that allows scale-up application and, despite of still high investment costs, is getting accessible to a larger community of patients worldwide. Tools and equipment are further improved to account for uncertainties, to enable proton therapy for moving tumours, hypofractionated proton therapy, FLASH proton therapy and proton therapy minibeams (Krieger et al. 2022; van de Water et al. 2019; Mazal et al. 2020). Moreover, international collaborative efforts are needed to gather a large European/extra European community to build the evidence and harmonize practices to deliver verified data for evidence-based medicine.

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4 Research needs in technology and medical physics related to proton therapy

Research and development in technology and medical physics stimulate the growth of proton therapy. Progress in this field is needed not only to decrease the costs but also to improve the efficacy and to make the treatment possible for a broader group of patients. The chapter summarizes recent review publications, which are paving the way of future research in this area.

4.1 Proton accelerators

4.1.1 Motivation

Currently there are only 61 operating PT facilities in the world, addressing only 3-5% of the clinical demand. This tremendous demand-supply gap is due to prohibitively expensive construction ($150-250M) and annual operation (~$10M/year) of a PT centre. Single-room solutions are slowly becoming available at $30-35M improving widespread adoption of PT. The size, cost (capital and operating), and complexity of accelerators for PT is clearly a significant impediment to reducing the cost and increasing the accessibility of PT. The new, inexpensive treatment units based on new accelerators will make PT widely accessible, thus creating a market potential in excess of $2B/year worldwide.

4.1.2 Status

Currently, the vast majority of PT centres are operating 230-250 MeV synchrotrons, cyclotrons or small synchrocyclotrons. The advantage of cyclotrons lies on magnets of reasonable size, due to relatively low beam rigidity, and dedicated shape design, which enables overcoming relativistic limitations. To reduce the energy, mechanical absorbers of different thicknesses are used, which produce neutrons and lead to activation of the surrounding area. Synchrotrons the extract the required energy (down to around 70 MeV), a process which takes a relatively long time and results in a prolonged treatment time. In the last decade a significant R&D has been performed to improve accelerator technology (Eickhoff, Weinrich, and Alonso 2012). The concepts required to make PT “smaller, lighter, and cheaper” are broadly discussed in literature (Jongen 2010).

Compact superconducting synchrocyclotrons were introduced into the clinical practice after 2015 and allowed for decrease the size of treatment facilities and for the reduced energy consumption. Here the progress was possible due to developing of high magnetic fields based on new superconductors. Ion Beam Application (IBA, Louvain-la-Neuve, Belgium) introduced the single-room PT system “Proteus One” based on a synchrocyclotron (S2C2) with a 220 degrees rotating gantry and weight of 50 tons. Advances in superconductor (Nb3Sn) applications allowed to achieve magnetic field of 8.7 T and to decrease the weight of the Mevion S250 (Mevion Medical Systems, Littleton, MA, United States) synchrocyclotron to 17 tons. However, the main drawback of cyclotrons and synchrocyclotrons is the fixed beam extraction energy

At present several hospital-based PT centres are **synchrotron**-based and offer advanced beam delivery systems employing raster-scanning or range-stacking techniques. This solution is extremely attractive

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considering that the beam energy can be adjusted in a range between 70 and 250 MeV and, due to a slow extraction method, the beam can be generated within seconds. Synchrotrons are able to perform fast 3D raster scanning target irradiation optimized up to 255 different energy steps, which allows for high-performance treatment of moving. Clinical commercial solutions based on synchrotrons are nowadays available representing a mature radiation therapy tool.

The **Dielectric Wall Accelerator** (DWA) was proposed at the Lawrence Livermore National Laboratory to produce pulsed proton beams suitable for PT. DWA is proposed to use transmission lines to supply a traveling electric field to a high gradient insulator. The required accelerating gradient is obtained on a high gradient insulator (HGI) beam pipe with stacked transmission lines, driven using optical switches. The HGI should demonstrate high breakdown field stress, up to 100 MV/m, approximately 5-10 times more than in conventional insulators. It is assumed that DWA will be able to accelerate protons to 200 MeV in nanosecond pulse lengths. This system is potentially advantageous as proton beams could be delivered with modulation of energy, beam current and spot size on a shoot-to-shoot basis. An engineering prototype has been constructed by the Compact Particle Accelerator Corporation (CPAC, Livermore, CA, United States) and initial experiments have been conducted but no final success was achieved. The system will be significantly cheaper both in investment and due to low energy consumption.

Although the application of **linear accelerators** (linac) to PT has initially been proposed in the 1990's, the research on radio frequency linac has been intensified in the past decade as it benefits from the availability of relatively inexpensive and reliable klystrons (of 3 GHz). Several concepts for linacs for PT were developed in the frame of TERA, a Foundation for Oncologic Hadrontherapy based in Italy and at CERN. Within TERA, the Cyclinac group has developed the project TULIP (TUrning LInac for Proton therapy), in which either a commercial cyclotron could inject protons into a linac mounted on a structure rotating around the patient or, the *all-linac* solution, with the length of the rotating structure reduced by a factor of two (Cuccagna et al. 2018).

Development of 750 MHz radiofrequency quadrupoles at CERN (Vretenar et al. 2014) allowed for construction of proton linac by CERN spin-off company ADAM (Advanced Oncotherapy, Geneva, Switzerland). In this system, 5 MeV protons are injected into a 3 GHz drift tube linac and accelerated up to 230 MeV. Its modular construction allows for beam delivery for a given energy up to 230 MeV for image-guided hadron therapy (Degiovanni, Stabile, and Ungaro 2016). The advantage of this system is the possibility for extraction of the required energy and the very small proton spot size, which will result in better dose conformity. The first accelerator is in operation in London but it is still not used for patient treatment.

In the last decades, **ion acceleration from laser-plasma** interaction has become a popular topic for multidisciplinary applications and has opened new scenarios in the PT framework, representing a possible future alternative to classic acceleration schema. A dedicated laser-generated proton beamline was built at the Extreme Light Infrastructure (ELI) Beamlines Facility (ELI) at Dolní Břežany, Czech Republic. The laser driven accelerating systems produce protons in very short, femtosecond long pulses, which are of great interest for potential FLASH therapy. A dedicated line for beam transport,

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dosimetry and irradiation is to be installed there for research purposes. However, at this stage of the development the laser generated proton beams are still not ready for clinical applications.

4.1.3 Research needs

The research and development on dielectric wall accelerators should be continued. This is still a high-risk project but the technology has the potential to be a game changer, because of the low cost, small size of the accelerator and low power consumption. Development of new isolators with very high breakdown field stress would be of importance.

Introduction of the compact superconducting synchrocyclotrons significantly decreased the investment and operation costs of the single-room PT systems. The further decrease of the size (weight) of the synchrocyclotron would be possible when higher magnetic fields could be generated. For this, new superconductors are needed with higher critical current. Nowadays R&D programs for future a collider at CERN can advance the technological issues for the reduction of size and cost of these accelerators for PT.

A realistic assessment of the further development of the laser-driven proton accelerators is needed. Operation of laser driven beam lines require high-level clean rooms (ISO7 clean room), which might be difficult in clinical conditions. It should be demonstrated in what cases these facilities can compete, in terms of investment price, operational price, type of tumour treated, with the conventional PT accelerators. In the EU project HIL PT System a patented approach to particle acceleration and beam delivery, combining nanotechnology with ultra-high-intensity lasers and novel magnetic design is further developed. These technological breakthroughs enable meaningful reduction in size of up to 50%, saving hospitals valuable space and requiring less initial investment on setup labour.

Moreover, particular attention has to be paid in novel approaches on typically gantry-based beam delivery systems. Even for those, a reduction in cost and size can be obtained in the future by applying novel superconducting materials as already mentioned in this paragraph. We have to underline that half of the cost of the PT facility is related to the beam delivery system. R&D programs in this field have to be strongly supported even considering that in the field of accelerators, the perspective to develop innovative solutions, is extremely limited from laser-plasma acceleration.

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4.2 FLASH

4.2.1 Motivation

The aim of radiotherapy is to irradiate tumours with photons, electrons, protons or heavier ions and kill cancer cells while safeguarding healthy tissues. The latter, especially near the tumour, unavoidably receive a part of the radiation dose and may suffer damage, which can lead to side effects. Conventional radiotherapy uses a variety of strategies to protect healthy structures. Fractionation is a common method to widen the therapeutic window: the region between the normal tissue complication probability (NTCP) and the tumour control probability (TCP) curves (Figure 1). Patients typically receive a daily small fraction of the total treatment radiation dose, on average 20 to 30 fractions of around 2Gy (Gray = Joule/kg), with dose rates of 0.1Gy/s. Thus, normal tissues can be repaired before the subsequent radiation dose is administered with limited effect on the tumour control.

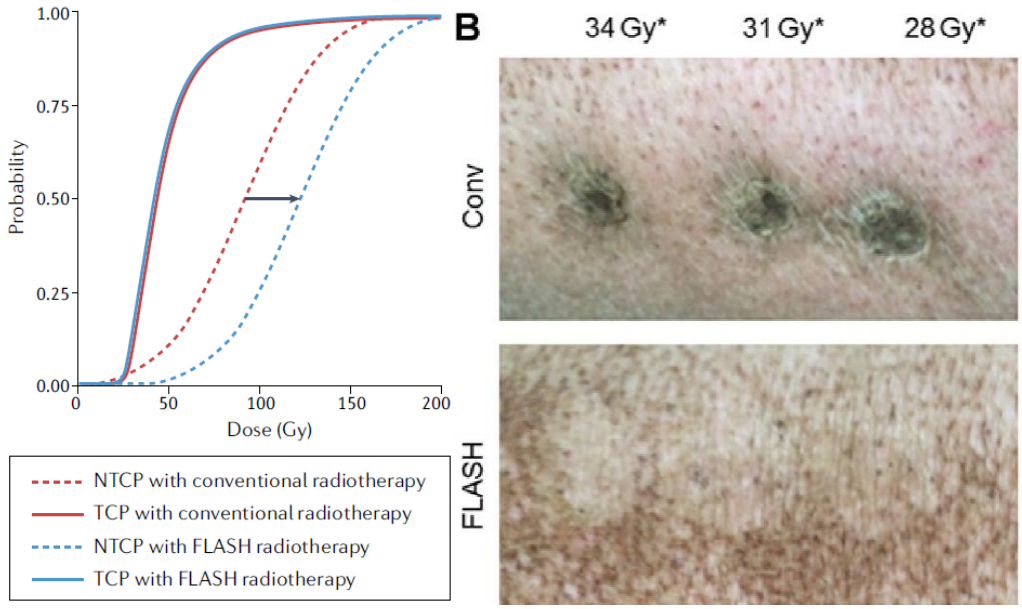

Figure 1. A: The therapeutic window. Radiotherapy seeks to widen the separation between the curves of tumour control probability (TCP) and normal tissue complication probability (NTCP) to increase the tumour dose while avoiding toxicity. With FLASH, while TCP is maintained, the NTCP curve is shifted to the right (black arrow): higher doses are needed for the same probability of complications. B: Severe tissue lesions in conventionally-irradiated spots and the normal appearance of the skin in FLASH-irradiated spots. Adapted from (Vozenin, Bourhis, and Durante 2022; Vozenin et al. 2019).

Different studies, dating back to the 60's (Town 1967; Nias et al. 1969; Hendry et al. 1982), have shown that if instead of low, very high dose rates are used (exceeding 50 Gy/s), healthy tissues exhibit less damage, Figure 1B, while the effect on tumours is unchanged, thus, increasing the therapeutic window. This practice, called "FLASH radiotherapy" as the total prescribed radiation dose is delivered in less than a second, has been recently revisited, replicated and shown very significant normal tissue sparing factors (Favaudon et al. 2014); it offers clinicians the opportunity to improve radiotherapy by reducing adverse side effects. FLASH is now considered as one of the most promising breakthroughs in radiation oncology. It is however, in the early stages of development.

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4.2.2 Status

Most pre-clinical studies investigating the FLASH have used electron radiation fields generated by dedicated or modified clinical accelerators that produce radiation pulses of an ultra-high dose per pulse. Compact apparatuses for photon FLASH are under development and the main vendors of proton therapy system, i.e. Varian (Varian Medical Systems, Palo Alto, CA, USA) and IBA, have both announced large initiatives on FLASH. Clinical PT systems were not designed for FLASH but they are able to perform ultra-high dose rate irradiations after machine commissioning tests. Clinical proton research has also been reported with hybrid systems that employ patient-specific 3D-range modulators and ridge filters (Simeonov et al. 2017; Yokokawa et al. 2019). Furthermore, ion acceleration from laser-plasma interaction has become a popular topic for multidisciplinary applications and opened new scenarios in the PT framework, representing a possible future alternative to classic acceleration schema. The high-intensity dose rate regime that can be obtained with this approach is attractive to the radiation oncology community. The laser-plasma accelerators field is rapidly evolving thanks to the continuing development of high-power laser systems, thus allowing the investigation of the interaction of ultrahigh laser intensities (>10^{19} W/cm2) with matter. Because of such interaction, extremely high electric and magnetic fields are generated (>100 GeV/cm) that allow particle acceleration at relativistic energies. Many laser facilities carried out experiments on ion acceleration, exploring different regimes of laser interaction with a variety of targets, which gave rise to the proton beam with the energy of about 100 MeV from nm-scale foils of solid density.

As treatment outcome strongly relates to the delivered radiation dose, measurement of the ionizing radiation dose plays an important role in all steps of the radiotherapy workflow. However, FLASH conditions are challenging for dosimetry. Active detection systems suffer from saturation and need high correction factors for recombination losses due to much higher dose rates per pulse, in comparison to conventional beams. Although passive dosimeters are not affected by the ultra-high dose rate, they are incompatible with existing clinical recommendations, they do not provide real-time results and they are impractical due to manual and long read-out procedures. Dosimetry for FLASH requires high time resolution and a wide dynamic range for monitoring high doses and dose rates. Prototypes of suitable active detectors exists, e.g. very thin ionization chambers, solid state detectors, diamond, chemical and luminescent dosimeters, but they still require research before clinical introduction (Gomez et al. 2022; Cimmino et al. 2022; Verona Rinati et al. 2022; Schuller et al. 2020). Currently, methods of measurement systems for time resolved dose-rate in clinical settings are inexistent. Furthermore, FLASH treatment planning should consider the dose-rate time structure in calculations and validation measurements and the optimization of additional parameters, i.e. beam current and scanning speed (Felici et al. 2020; Higginson et al. 2018).

Different experiments have been conducted to observe early biological response of proton FLASH in laser and RF accelerators, with dose rates ranging from 10^3 to 10^9Gy/s (Durante and Paganetti 2016; Durante, Orecchia, and Loeffler 2017). Although dose rate effects were not observed for in vitro assays (Diffenderfer et al. 2022; Jolly et al. 2020), there were indications of differential response according to the temporal structure of the proton beam, i.e. pulsed, continuous, delayed pulse (van de Water et al. 2019). Embryonic investigations on survival and induction of morphological malformations on

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zebrafish did not show significant influence of proton dose rate but acute radiation effects were reduced (Beyreuther et al. 2019). In vivo experiments in the proton plateau region showed toxicity-sparing effects in the skin, muscle and bone of mice and dogs; at the spread-out Bragg peak (SOBP), a protective effect was shown in abdominal irradiation in mice and dose rate escalation studies revealed neurocognitive sparing (Evans et al. 2022). However, negative FLASH effects have been observed in acute-responding tissues, i.e. blood, intestine and abdomen and the sparing effect has been only observed in vivo. Although the reason is not yet clear, several factors might have contributed, e.g. differences in dose rates, volumes, beam parameters, simplified dosimetry and setups. Thus, further research is necessary. On the other hand, consistent results have been observed for tumour control on short- and long-terms, from simple subcutaneous models to complex orthotopic and genetically engineered models (Liljedahl et al. 2022). These studies support the idea that tumour control does not depend on dose rate: malignant tissues are equally sensitive to FLASH and conventional RT in terms of DNA damage but many radiation-induced biological mechanisms are not activated in FLASH conditions on healthy tissues, there is less DNA damage and consequently a reduced inflammatory response (Levy et al. 2020). The latter effect may be important for combining FLASH with systemic therapies (Durante and Formenti 2020).

The differential response between malignant and non-malignant tissues has been historically related to the role of oxygen and reactive species; non-malignant tissues have much lower oxygen levels than most tumours (Taylor et al. 2022). It has been hypothesized that FLASH may induce rapid oxygen consumption and lead to local transient depletion (Wardman 2020), which is protective to non-malignant tissues as high oxygen levels do not favour the FLASH effect (Montay-Gruel et al. 2019). Besides oxygen, other hypotheses point towards the role of tumour microenvironment, immune response and the sparing of immune cells (Jin et al. 2020). With no conclusive theory: further investigation is paramount.

Curative FLASH has been researched with photons on domestic cats and mini-pigs, and with protons on dogs and mice, with initial safe, effective results, no short-term toxicity and long-term tumour control (Velalopoulou et al. 2021). However, a cat trial on its Phase III was halted due to late FLASH radiation-induced toxicity, possibly associated with the treatment protocol (single frontal beam, high dose, no bolus, inadequate dose-rate). Thus, considering long-term follow-up, fractionation and consistent beam parameters is crucial for clinical translation. In 2019, the first human patient underwent a successful FLASH radiation therapy (Bourhis et al. 2019). The patient received one fraction of electrons in 90 ms of 10 pulses with 1.5 Gy/pulse (mean dose rate: ~167 Gy/s). An electron dose-escalation trial, IMPULSE (NCT04986696), is ongoing for skin metastases to evaluate the maximal tolerated dose associated with acute/late toxicity and tumour control. In this trial, the dose per pulse is increased while the number of pulses and overall treatment time is kept constant. The first proton clinical trial, the FAST-01 at Cincinnati Children's PT Centre, used dose-rates superior to 40 Gy/s for palliative treatment of extremity bone metastases. FLASH-PT clinical feasibility and safety were verified, with minimal adverse events and a similar efficacy in pain relief as the standard of care (Mascia et al. 2023).

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4.2.3 Research needs

There are still various open questions around FLASH radiotherapy. The mechanism itself that causes a differential tissue response is not completely understood. There is little evidence on the complex physical and radiochemical processes that happen around the DNA in very short time scales and the role of oxygen (and other radiochemically-reactive species) in FLASH conditions. Dose and dose rates still have to be identified for specific endpoints. Further research is required on late radiation-induced response, volume effects, fractionation, re-irradiation, interaction with the immune system. Preclinical trials have not been standardized for their biology and physics aspects: mostly with a single radiation modality, different models for tumours and normal tissues, different biological assays, dosimetry, imaging, dose verification, treatment planning systems, data analysis and storage methods. In addition, the FLASH effect may be different for different radiation beams, the pulse structure may affect the outcome and temporal and spatial modulation for scanned beams may complicate FLASH therapy.

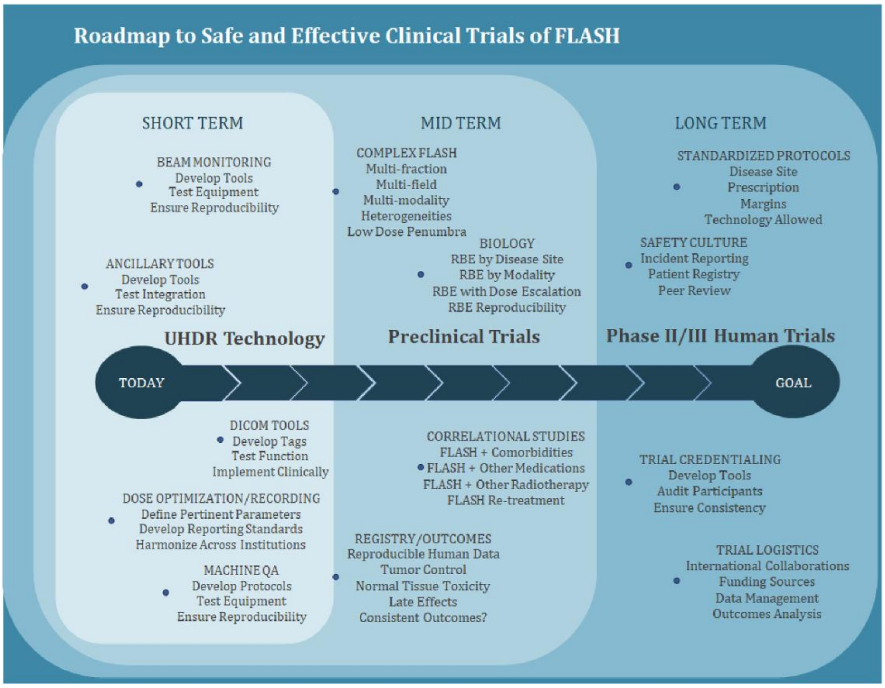

Figure 2. A roadmap highlighting key components for successful Phase II/III clinical trials in humans. Many of the technological issues are being actively addressed, while preclinical trials are still being organized and standardized. From (Taylor et al. 2022).

Scientific organizations, i.e., ESTRO, AAPM, ASTRO, National Cancer Institute (NCI), IAEA, EFOMP and vendors, e.g. SIT (Sordina IORT Technologies, Vicenza, Italy), IntraOp (IntraOp, Sunnyvale, CA, USA), Varian, IBA, are actively trying to bridge recommendations and technological gaps to allow clinical trials on FLASH. There are, however, important issues involving safety, dosimetry and treatment planning that still hamper clinical compliance and may affect trial results. In terms of safety, calibration procedures for absolute dosimetry, dose-rate reproducibility and independent active dose monitoring are paramount aspects of precise radiotherapy but still in development FLASH. Machine stability and beam monitoring are key factors for any RT treatment but quickly stopping a FLASH beam to avoid

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mistreatment is very complex, due to the temporal structure of the beam and the intense dose rates, for which no commercial system has published compliance. Moreover, guidelines and recommendations are not harmonized, sometimes they differ within the same country, and they may limit commissioning experiments, e.g. due to annual dose requirements. Robust treatment planning strategies to account for specific motion and consider the dose and dose rate to reach the therapeutic ratio need to be developed. Imaging is also essential for target localization, real-time monitoring and positioning, as small misalignments can significantly affect the dose distribution and local dose rates.

As a roadmap to FLASH clinical trials (Figure 2), Taylor (Taylor et al. 2022) defined for important questions to consider for treatment reproducibility and patient benefit:

1. “Can we fully define, optimize, deliver, and store a FLASH plan’s delivery history in a standard fashion so that all needed parameters are recorded for later review?”

2. “Can we measure if the biological response to FLASH treatment varies from patient to patient and from tumour to tumour from day to day, in particular if medications or drugs vary the critical biology of FLASH therapy?”

3. “Can FLASH treatment be delivered across realistic, deep and/or larger volumes?”

4. “How easy will it be to introduce FLASH therapy into the overall care matrix of a patient?”

Although it might still take time before we can answer all these questions, it is important to look for solutions as a community and focus on understanding the mechanism, finding the optimal irradiation parameters and developing technologies for clinical implementation and dosimetry.

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4.3 Technologies for reduction of range uncertainties

4.3.1 Motivation

The characteristic dose deposition of protons presents superior conformity with respect to the traditional photon approach; protons slow down while penetrating tissue, deposit most of their initial energy toward the end of their range, and completely stop within the patient (Figure 3, top). This behaviour favours a sharp dose fall-off at the distal beam edge and a lower integral dose (Engelsman, Schwarz, and Dong 2013). To benefit from PT and to exploit the dose gradient behaviour, uncertainties in the proton range within the patient must be addressed, as sharper gradients (Figure 3a, bottom) are also less forgiving with positioning, and thus dose errors (Knopf and Lomax 2013).

Range uncertainty can directly affect radiotherapy efficacy and toxicity (Figure 3 b). If the planned and delivered range differ, it is possible to slightly under-shoot the tumour and, due to the sharp distal fall-off, produce under-dosage that may lead to unsuccessful treatments and recurrences (Lomax 2020). Clinically, this effect is decreased by the use of treatment margins or robust optimization, which, to a certain extent, also mitigate the benefits of PT with increased irradiated healthy volumes (McGowan, Burnet, and Lomax 2013). Range uncertainty can also affect dose homogeneity within the target, promote hot and cold spots and, in the other direction, range errors can cause over-dosage to healthy structures abutting the tumour. The latter may trigger different levels of toxicity, side effects and secondary conditions.

4.3.2 Status

Multiple techniques are used to verify the proton range within patients or to account for the effect of its uncertainty on the dose distribution, which can be related to the TPS, imaging and monitoring. Treatment planning-based strategies use probabilistic or robust optimization to maximize both the target coverage and the organ-at-risk (OAR) sparing considering a variety of setup and range error scenarios. They assign probabilities to the error scenarios and optimize the expected plan quality or determine best dose distribution for the worst error scenario (Korevaar et al. 2019).

Imaging-based methods aim to reduce uncertainties related to the image used on treatment planning, as the proton range is sensitive to patient modelling. PT dose calculations require accurate knowledge of both the stopping power ratios (SPRs) and the mean excitation potential (I-values) of tissues. Traditionally, the patient CT (in Hounsfield units, HU) is used to derive SPRs, through a HU-to-SPR calibration curve (Schneider, Pedroni, and Lomax 1996). However, tomography presents several limitations, e.g., noise, beam hardening, reconstruction artefacts, that contribute to HU uncertainty and affect the HU conversion into stopping power. The calibration curve method also has shortcomings, as materials with the same SPR may have different HU values and it does not yield I-values (Mohan, Das, and Ling 2017). Furthermore, anatomical variation (e.g., organ motion, tumour regression, weight loss, or varying filling of internal cavities) and daily patient misalignments produce rigid translations, rotations and deformable changes that are likely the largest source of range uncertainty (Hoffmann et al. 2017). All these factors affect the dose calculation accuracy and increase the range uncertainty up to the centimetre range (Lomax 2020; Yang et al. 2012). Most proton centres

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use a range uncertainty of 2.5-3.5% of penetration depth, plus additional 1-3 mm for delivery system, biological, and geometric uncertainties (Mohan, Das, and Ling 2017).

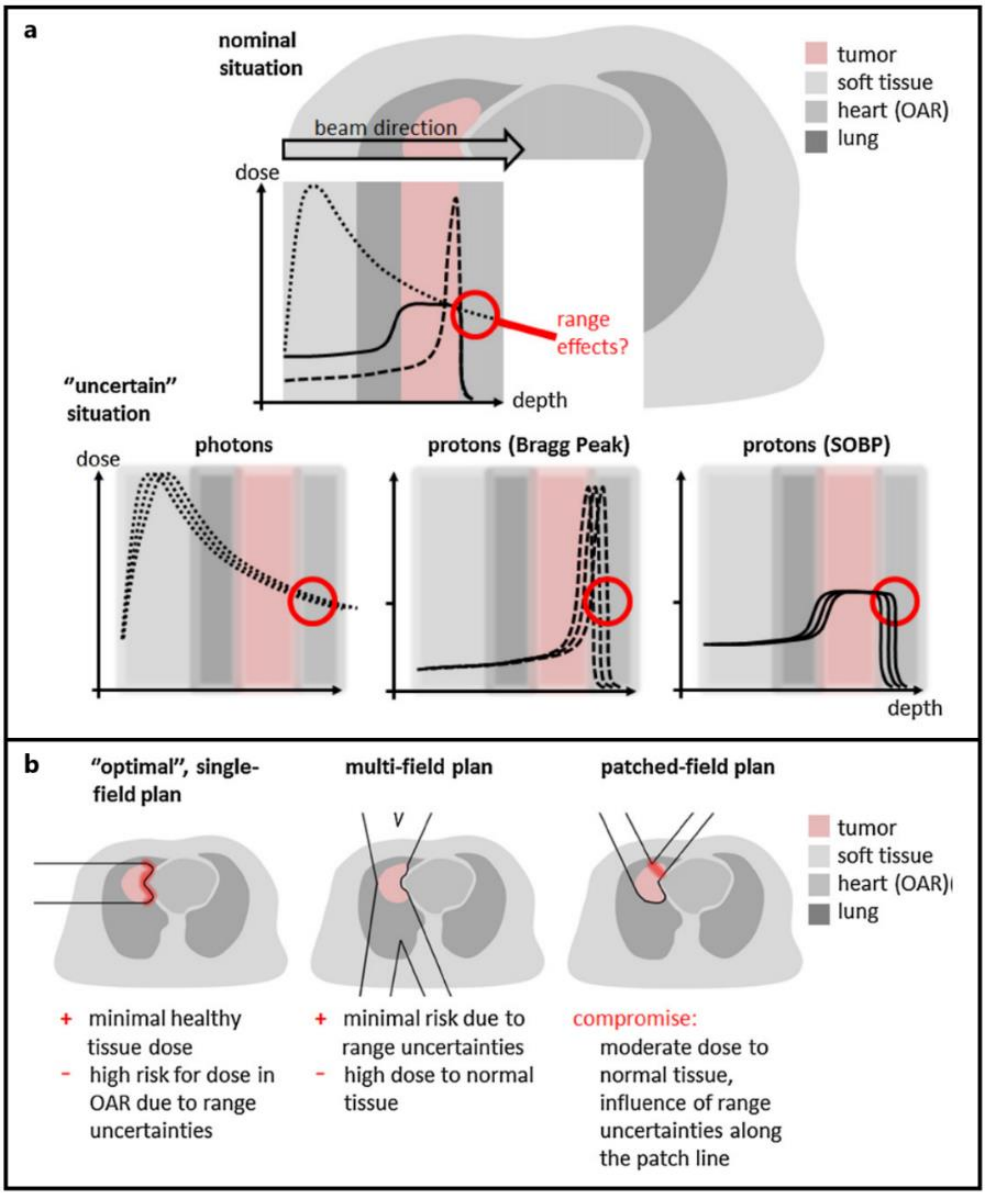

Figure 3. (a) Top: Potential dose benefit of a proton treatment compared to a photon treatment (dotted line: photon depth-dose curve; dashed line: mono-energetic proton depth-dose curve known as Bragg Peak; straight line: spread out proton Bragg curve (SOBP) to cover the whole tumour). Bottom: Influence of uncertainties to these depth dose curves. (b) Different planning strategies for proton therapy and their potential sensitivity towards range uncertainties. Adapted from (Knopf and Lomax 2013).

As conventional CT does not provide all the necessary data for accurate SPR determination, different centres have adopted Dual-Energy CT (DECT), which adds a layer of information, by including a second imaging energy. With DECT, it is possible to determine the effective atomic number (Z_{eff}) of tissues and consequently to derive I-values using a heuristic conversion. DECT has been shown to provide more accurate SPRs than conventional single energy spectrum CT scans (Bär et al. 2017). Additionally, it has

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shown improvement in treatment planning absolute range prediction from 3.5% to 2% or less in specific geometries (1.7% for brain-tumour treatments), which can enable a safety margin reduction of 35% and decreased integral and OAR doses (Peters et al. 2022).

A number of in vivo range verification techniques have been proposed with measurements of dose, fluence or indirect surrogate signals from the proton irradiation. Among them proton radiography or CT, which allows more direct measurements of relative stopping powers than DECT (Tattenberg et al. 2022), prompt gamma, PET and MRI have been developed and, to different extents, translated to the clinical environment. Although application is often challenging, they can offer real-time possibilities without (or with limited) additional radiation dose often in the same geometric referential as the proton treatment.

Proton radiography measures the residual range from higher energy protons detected on exit from the patient. To obtain improved spatial resolution, the entrance and exit coordinates of each proton is detected in coincidence with the range measurement. It presents high contrast, decreased imaging dose, it has limited spatial resolution (due to multiple Coulomb scattering) and it directly provides tissue stopping power values (Knopf and Lomax 2013). Proton transmission images can be taken under the same geometrical conditions as the treatment for each fraction and, besides range verification, they can be used for patient positioning, adaptive planning and be extended into proton tomography. In addition, proton-integrating radiography (range probing) is used to directly compare the spot-wise measured depth-dose curve with an expectation derived from dose calculation (Wohlfahrt and Richter 2020).

Techniques based on measurement to verify the exact position protons stop in the patient have been in development since the early stages of PT. As protons penetrate tissues, they cause nuclear reactions due to inelastic collisions. According to their initial energy, protons may excite the target nuclei or generate positron-emitting isotopes (e.g., ^{11}C, ^{13}N, ^{15}O). Since the 1970's the latter phenomenon has been investigated and foreseen as a surrogate for delivered dose reconstruction (Bennett et al. 1978). The positron-emitting isotopes can recombine with a surrounding electron from the tissue and emit two coincident gammas, which can be detected outside the patient, Figure 4a. Although this effect is observable both with in-beam and commercial PET scanners, technological limitations have hampered the establishment of this technique.

In-beam detectors are not commercial as they may cause beam interference, due to radiation effects on electronics and additional treatment time (Pausch et al. 2020). Commercial PET scanners from nuclear medicine have been used for research and clinically but they are not ideal for range verification. It is an offline approach, in which the patient is transferred to the diagnostic room and is subject to positioning changes and physical and biological washout effects between irradiation and imaging (Paganetti et al. 2021). In addition, the PET signal is always delayed with respect to the beam delivery due to the half-life of the reaction products. Direct range verification by dose and activity profile comparison is also complex, as the activation depends on the target elemental composition, threshold energies and the activity distribution variation according to the imaging timing and different isotope half-lives (Paganetti and El Fakhri 2015).

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Besides the positron-emitting isotopes, the above-mentioned excited nuclei can also be used for range verification purposes. By returning to their fundamental state, each unstable nucleus emits a fast and energetic prompt gamma ray. This process happens along the proton beam penetration path, prior (<3mm) to the Bragg-peak (Knopf and Lomax 2013). Range inferences come from prompt gamma measurements, as they are correlated with the penetration path. This technique also has technological challenges due to the high energy of the prompt gamma emissions and detector development research is still ongoing. Nevertheless, IBA has developed a knife-edge slit camera for range monitoring in clinical treatments that can detect local range shifts down to 1-2 mm but the collimator is large and prone to affect both patient positioning and clinical workflow (Pausch et al. 2020; Paganetti et al. 2021), Figure 4b.

MRI is another technique used to visualize radiation-induced tissue changes in tissues, which can reveal in vivo delivered dose distributions. It has the advantages of availability, no additional radiation exposure and high spatial resolution, in particular for soft tissues, for which CT is not ideal. However, at its current stage, it is an offline strategy, which relies on dose-response relationships.

4.3.3 Research needs

Research on imaging-based technologies is ongoing. For proton CT, a promising technique for *in vivo* SPR determination, the current applications are limited to cranial sites, due to energy specifications, as proton beams with sufficient energy to traverse large body regions are not always available and due to severe image artefacts (Wohlfahrt and Richter 2020; Alkadhi et al. 2022). Clinical proton radiography suffers from the complexity of integrating imaging and therapy systems, as the required proton current for imaging is orders of magnitude lower than for therapy and all detector systems and safety devices are designed for high proton currents in therapy. Conventional CT is moving towards the use of energy-resolving detectors, for spectral separation into energy bins, which have shown superior accuracy in SPR and material assignment with respect to DECT, but it still requires spectral de-noising, beam hardening and scattering corrections (Wohlfahrt and Richter 2020; Pausch et al. 2020; Paganetti et al. 2021). Thus, research and development on image processing and reconstruction techniques is likely to remain prolific and benefit CT and radiography for PT.

For prompt gamma and PET methods to reach the clinical environment, research efforts have been focused on scintillators, photo-counting devices, image acquisition and processing speed. The latest PET scanner generation is based on scintillation crystals and dynamic photon counters that can reach sub-mm reproducibility on distal range measurements (Ferrero et al. 2018). Further development is necessary on background suppression, prediction models (still at the level of a few millimetres), management of the pulsed beam time structure and signal acquisition from short-lived positron emitters (Paganetti et al. 2021). For prompt gamma camera detection systems large improvements were made on collimation, position-sensitive scintillation, solid-state photomultiplier readout, gamma spectroscopy and more comprehensive prediction models. Some clinical systems still require a better positioning accuracy and efforts are ongoing on background suppression, reconstruction techniques and prediction modelling, including time-of-flight approaches that focus on the arrival time of photons (Hueso-Gonzalez et al. 2018; Xie et al. 2017; Krimmer et al. 2018).

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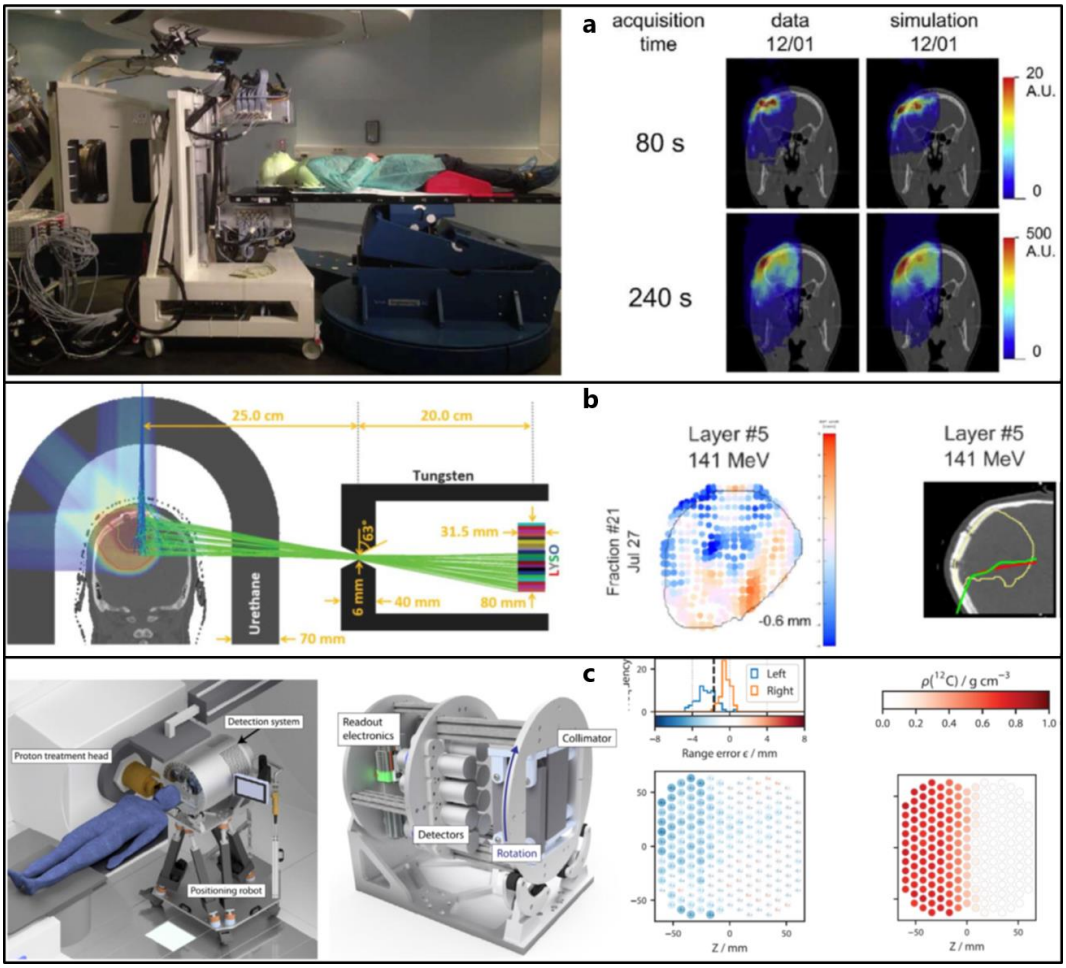

Figure 4. Figure 4– a: Example of the dedicated in-beam PET scanner in treatment position and the dynamically reconstructed PET activation data in comparison to the simulated predictions in two different time windows during proton beam delivery. The PET images (colour wash) are superimposed onto the planning x-ray CT (grey scale). b) Schematic of the knife-edge slit camera, projecting the prompt gamma signal (green) from the proton beam (blue) onto the position sensitive scintillators beyond the collimator. The corresponding analysis results in the spot-by-spot (with aggregation) range difference comparison in beam-eye-view as well as prompt gamma-based estimation of the measured (green) and predicted (red) Bragg peak depth overlaid with the planning CT for a given energy layer and treatment fraction. c) Schematic of a spectroscopic system integrated in the proton beam gantry for a representative treatment position, along with the details of the energy- and time-resolved detector components beyond the collimator. The results enable quantifying the range difference from a prediction model for each applied spot along with carbon and oxygen concentrations, in this example obtained when inserting a slab phantom on the left of the beam path in water (with spot aggregation). Adapted from (Hueso-Gonzalez et al. 2018; Xie et al. 2017; Fiorina et al. 2018).

Both technologies still require clinical evaluation, further design and acquisition development. Neither are they optimal for tissue heterogeneities or large tumour sizes, nor have they integrated imaging for anatomical registration or patient modelling. As prompt gamma collimation can be impractical, efforts are ongoing to move towards different technologies, e.g. Compton cameras based on solid-state detection or hybrid systems to consider the signal from PET, prompt gamma and triple coincidences (Hueso-Gonzalez et al. 2016). Besides range verification, the latter could promote tumour localization or image-guidance during treatment (Lang et al. 2014). Furthermore, prediction models are likely to benefit from accurate experimental measurements of cross section data and advances in AI. For

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availing from the benefits of the different techniques, i.e. the range localization accuracy, real-time and use of tracers, future research is likely to focus on technology integration and optimization to capture the nuclear reactions during and after irradiation.

Complementary techniques are also under development for specific disease sites. As an example, the use of thermoacoustic phenomena, the so-called ionoacoustic signal, promises a means for in vivo range verification during treatment and possible correlation with ultrasound imaging of the tumour morphology (Lehrack et al. 2020; Takayanagi et al. 2020). Although detector design is still under development, acoustic transducers can potentially provide highly accurate information for a huge dynamic range on energy loss, straggling, lateral scattering and water equivalent thickness, with the advantages of being insensitive to gamma and neutron radiation (and the background they create), with a detector medium unaffected by radiation damage. Other techniques and improvement on in vivo signal analysis may enable biology-driven treatment personalization for adaptive therapy; allow novel beam arrangements that properly avail from the steep dose fall-off, e.g. by placing Bragg peaks on the target's distal edge. Finally, as Monte Carlo (MC) simulations are heavily used to validate measured distributions of secondary particles, the accuracy of the MC codes and their ability to model nuclear interactions and the resulting secondary particle production is also crucial to the development of this field (Kraan 2015). The different tools available are mentioned in the previous sections and summarized in Appendix 2.

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4.4 Image guided PT and motion management in PT

4.4.1 Motivation

Current clinical available technology for image guidance in PT (IGPT) is majorly based on orthogonal X-rays for visualizing internal bony anatomy or fiducials. In the newest commercial PT systems, on-board cone-beam computed tomography (CBCT) has become available to visualize the internal anatomy of the patient with decent soft-tissue contrast. Because soft tissue changes along the beam path are more easily visualized with CBCT imaging compared to super positioning planar X-ray imaging, its use in PT will increase even further. An investigation of EPTN WP4 (Bolsi et al. 2018) has revealed that a considerable amount of treating centres were not equipped to perform CBCT imaging and retrofitting was most often not possible because of hardware limitations in gantry design. The main reasons for the lack of CBCT on systems was the lack of clinical release before 2014 on commercial systems. From 2014 onwards, most often CBCT was available in centres starting to treat patients with commercial proton systems. IGPT is conversing rapidly towards 3D volumetric image guidance solutions available from photon therapy. Although IGPT is still lagging behind compared to photon therapy image guidance (IGXT) solutions, especially in terms of scatter correction (iterative scatter correction) and rapidness of image acquisition.

In the reported literature, guidelines and roadmaps for IGPT are missing how to realize the catch-up of IGXT in particle therapy. Although initiatives are taken within organizations such as EPTN (WP4 Image guidance), AAPM and PTCOG (subcommittee imaging), no reports or guidelines are available at this moment. This is currently a limiting factor to allow proton centres to enable new technologies or methodologies for all aspects of offline and online imaging applications connected to the proton facilities.

The uncertainties in PT are mainly dominated by both intra- and inter-fraction setup errors and range uncertainty. The range uncertainty is estimated 3.5% based on single-energy (SE) CT imaging using stoichiometric calibration (Paganetti et al. 2021). Although the stoichiometric calibration method was developed in the 1990's (Schneider, Pedroni, and Lomax 1996), there is no clear consensus how the application or implementation into commercially available treatment planning systems should happen. With the introduction of dual-energy CT (DECT) imaging, uncertainty levels for range can be reduced (1-2%) compared to SECT for specific treatment sites (Wohlfahrt, Möhler, et al. 2017). Application of DECT to anatomical sites subject to breathing motion are more difficult to implement although dual-source systems scanning allow simultaneous DECT acquisition, i.e. 4D-DECT. However, manufacturing of dual source CT scanners can result in a limited field-of-view, with a diameter of approximately 30 cm, restricting full thorax scans in 4D-DECT. With DECT, treatment planning can potentially be conducted with a lower range uncertainty value during robust planning in proton therapy, reducing the dose to organs-at-risk (OAR). Although there are several scientific reports indicating improvement of SPR prediction by DECT (Wohlfahrt, Mohler, et al. 2017; Berthold et al. 2021), it seems that the consensus for HU-to-SPR mapping[9] with respect to all these innovative CT

[9] HU-to-SPR mapping is the process to transfer HU resulting from CT scans to stopping power ratios (needed to determine the range of the proton in tissue). A stoichiometric calibration based on biological tissues is still the

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modalities is still lacking and is it unknown how many PT centres apply DECT for HU-to-SPR mapping in the clinical routine. Possibly the clinical accessibility to DECT for SPR prediction will improve with recent commercial software release of "direct SPR" by Siemens AG. Recently, a more sensitive CT imaging process has been introduced in the clinic by the use of photon counting detectors. It is postulated that range uncertainties can be reduced further (below 1%) by photon counting CT compared to DECT (Paganetti et al. 2021) for SPR prediction.

When randomizing between photon and proton therapy in clinical trials, a relatively large amount of these trials show no significant difference in terms of clinical outcome. In fact, currently only for oesophagus a positive result was found during a randomized clinical trial comparing both modalities, i.e. reduced radiotherapy toxicity and postoperative mortality was obtained with PT while survival of oesophagus cancer patients in both arms was similar (Lin et al. 2020). For oesophagus cancer, a new consortium established, the PROTECTtrial to randomize between photon and protons (Hoffmann et al. 2022). Results on primary endpoints are expected in 2025.

It remains the question why so few clinical trials have demonstrated the superiority of PT. Many clinical treatment sites where it is difficult to demonstrate the advantage of PT are subject to strong soft tissue changes during the course of radiotherapy and potentially target motion with breathing (Liao et al. 2018). It is clear that the current clinical status of IGPT and motion management is still not optimal for all treatment sites. Robust planning on 4DCT has become available in commercial treatment planning systems but for PBS PT, it is not sufficiently adequate to assess interplay effects or impact of irregular breathing motion of the delivered proton dose. Conducting research in IGPT and motion management in PT can help to design new randomized clinical trials comparing photon with proton therapy and potentially obtaining an improved outcome for PT.

In the remaining part of this chapter, we will identify several topics that deserve further research and should lead to improved clinical outcome in proton therapy (and potentially surpassing photon therapy) in the domains of IGPT and motion management in PT, some of which are summarized in Figure 5.

4.4.2 Status

MRI- and Image-guided proton therapy

Because of the transition from passive scatter to pencil beam scanning particle therapy, the increased complexity has led to more sensitivity for soft tissue changes compared to the most complex photon therapy techniques. While in photon therapy, an expansion principle of the target has been used to incorporate uncertainties in the treatment process, **a simple margin expansion concept has proven to be inadequate in PT**. To incorporate the uncertainties originating from both setup and finite range, robust optimization concept has been implemented in clinical routine. Although this mechanism leads

current golden standard besides a relatively straightforward mapping based on calibrated plug phantom, such as the Gammex tissue characterization phantom 467 or CIRS electron density phantom. The result from a single energy CT is called SECT HU-to-SPR mapping. For a method that makes use of DECT, the HU-to-SPR mapping will be more accurate because, in very simple wording, two different energy spectra are better suited to solve an equation with 2 unknowns per voxel, i.e. electron density and atomic number.

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to adequate target coverage when proton treatments are subject to these uncertainties, robust optimization has the disadvantage of additional doses given to healthy tissues close to the target. An alternative to robust optimization or at least reducing the uncertainties related to setup error is to adapt the treatment plan online, based on the image of the day.

All steps that are needed in an online adaption workflow are still considered as research questions (Albertini et al. 2020). Regarding the increased use of CBCT imaging in treatment position, most progress has been made in facilitating CBCT-based online adaptive particle therapy majorly due to the availability of deformable image registration algorithms to convert CBCT into a virtual CT images suitable for proton dose calculation (Kurz et al. 2016). Clinical validation is still underway and only the first CE/FDA approved packages are becoming available in 2022-2023 for clinical use. Therefore it remains a research topic on the extraction of stopping powers based on CBCT images. Recent developments in photon therapy have led to the clinical implementation of a closed-bore linear accelerator with dedicated improved CBCT image quality, Ethos® from Siemens Health AG in 2020. **It seems evident that when proton versus photon randomized clinical trials are initiated also online adaptation modalities in proton therapy should become available.**

However, a roadmap towards online adaptive therapy based on CBCT is not yet in place in particle therapy, majorly because the CBCT is subject of additional patient-specific scatter that deteriorates not only image quality but also creates additional uncertainty on the conversion from HU to SPR and CBCT imaging can have a limited field-of-view. Because of the large heterogeneity of the treatment equipment of particle systems throughout the world it still has to be determined if a consensus can be reached or one unique methodology can be selected on how to use online CBCT images for dose calculation.

It is clear to the radiation oncology community that implementing online adaptive PT is urgent. Thus, several initiatives have been started within the EU since 2020 such as the RAPTOR consortium, an organisation of 15 partners focusing on clinical real-time adaptive particle therapy. **In total 12 research projects funded by EU H2020 investigate the way forward in real-time adaptation for particle therapy.** The ProtOnArt consortium is another initiative that for clinical implementation of online adaptive PT. However, in this consortium the partners have a specific in-room CT solution available to move more gradually from offline to online adaptive proton therapy. Compared to ProtOnArt, where the aim is first in-human online adaptive proton therapy, the RAPTOR project is considerably more fundamental in terms of the medical physics aspects and also covering a broader range of the topic, including the use of different online imaging modalities (including MR) and more advanced applications **towards time-resolved treatments for moving targets**.

The **quality management system** that should overview the online adaptive workflow in PT is still a major challenge. There are some similarities with online adaptive photon therapy workflows for patient-specific quality assurance (QA) and the possible solutions are similar. However, online adaptive particle therapy requires additional sensitivity, which deserves more attention compared to photon therapy. In particular, the conversion of online images to SPR requires verification on a patient level when the processes to generate virtual CTs are based on AI or deformable image registration. Online

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re-planning of complex PBS plans is potentially not the easiest path to clinical implementation of online adaptive PT. Alternatively so-called dose restoration, i.e. mimicking the treatment dose on a new online image, can be considered. However, it is currently not clear if dose restoration can be applied as an online adaptation strategy with sufficient quality management incorporated in the process. More investigation based on planning studies and clinical trials is required.

Because of the need for additional quality management procedures during online adaptive PT, the patient throughput will reduce compared to offline PT workflows. As such online adaptive PT will have to be combined with hypofractionation. However as was pointed out by Paganetti (Paganetti et al. 2021), online adaptive workflows will also mitigate setup errors and dose perturbations by soft tissue changes and as such facilitate the use of hypofractionation in PT compared offline workflows.

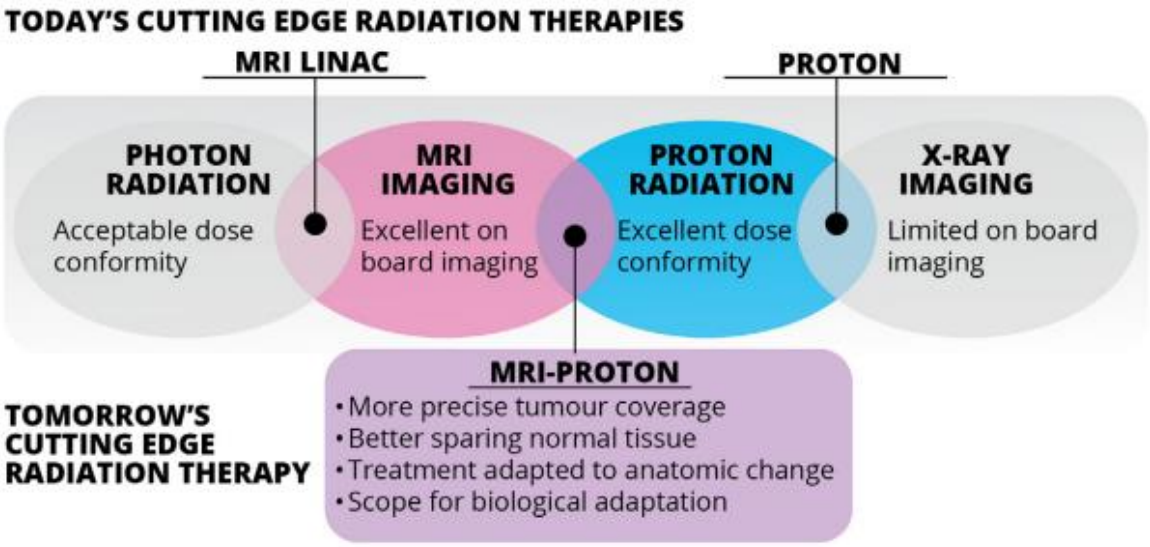

Figure 5. Combination of radiation and imaging modalities to reach most optimal situation. From (Pham et al. 2022)

Major research investment is needed to catch-up with photon therapy, when it comes down to implementing online MR-guided particle therapy systems. At the moment most probably no closed bore system (allowing the proton beam to reach the patient), no gantry and no robotic patient positioning system can be created for MR-guided PT (MRgPT) (Paganetti et al. 2021; Hoffmann et al. 2020; Gantz, Schellhammer, and Hoffmann 2022). The combination of proton therapy with online MR imaging enables an improved soft-tissue contrast, segmenting malignant cells from healthy tissues and as such, dose escalation with proton therapy can be facilitated by sparing these healthy tissues with the finite range of the proton beam (Keall et al. 2022). Potentially better clinical outcomes can be expected by delivering a higher biological effective dose while sparing close by organs at risk: for pancreatic cancer, the duodenum and small bowel could be better spared, for centrally located lung cancer, the bronchial tree, great vessels and for heart and for brain cancer, the brainstem and optic nerves. Recent developments in cardiac radiation ablation for ventricular tachycardia (VT) (Cuculich et al. 2017) have also brought PT forward as an option for ablative therapy to better preserve the healthy

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cardiac tissue (Widesott et al. 2020). With the realization of an MRgPT system, intrafraction monitoring can result in more safe execution of the VT ablation.

First MRgPT prototypes are being designed at the research facility of Dresden and Heidelberg, with the potential of realizing a clinical system at Dresden in the short term. Based on the history of MR-guided systems in photon therapy, it can be expected that roughly 10 to 15 years of additional research and development are needed before we can expect the first MR-guided PT systems for clinical treatments. However, the challenges in MR-guided PT systems are much larger than what has been seen in photon therapy. The conversion from an online 3D MR image of the patient in treatment position to a synthetic CT suitable for PT dose calculation will result in additional uncertainty of SPR with a few percent, compared with current PT dose calculation on CT and DECT. With the ongoing effort to use photon-counting CT for HU-to-SPR conversion this difference would only increase further, which indicates that more research efforts are needed for PT dose calculation on MR-only. Additionally, it seems important to limit MRI sequences to standard T1w, for instance, in order to reduce geometric distortion and allow the application of a universal MRI-to-SPR conversion (Hoffmann et al. 2020). Currently, the consensus is that deep learning by convolution neural networks will be required to conduct MRI-to-SPR conversion and this requires additional challenges to have a clinical validation of an MR-only workflow on MRgPT systems. Related to PT dose calculation for an MRgPT system, the deflection of the proton beam in the patient has to be modelled in order to obtain a correct quantification of the patient's received dose. A full functional treatment planning system is currently unavailable for PT dose calculation within an MR field nor the inverse optimization of beamlets to reach a therapeutic IMPT plan for an MRgPT system. In any case, there is an overwhelming amount of unanswered research questions when it comes down to MRgPT and this will require intensive collaboration between industry and research institutes.

One of the major drawbacks of MR-guided systems is the relatively low patient throughput (because of mandatory daily adaptations originating from first estimates of hardware designs for an MRgPT system) and this automatically leads to application of hypofractionation for MR-guided systems. However, hypofractionation is not yet clinically accepted in (paediatric) PT and, from the research on late toxicity effects from increased RBE and LET effects in the distal edge of the PT beam, more knowledge is required in the near future for the implementation of online MR-guided PT.

Motion management in proton therapy

There is a clear lack of sufficient guidelines in how to handle future developments in the domain of IGPT, **motion management in particle therapy summarizing by different reviews and the AAPM TG 290** (Rietzel and Bert 2010; Mori, Knopf, and Umegaki 2018; Li et al. 2022). The IROC (Imaging and Radiation Oncology Core) QA centre provides a lung phantom with a moving tumour in order to review photon and proton centres on their motion management protocol (IROC). PT centres in the USA are allowed to include patients in RTOG clinical trials, focussing on tumour sites where respiratory motion is expected, after obtaining the credentials for respiratory managed photon or proton therapy. As such, reported outcomes from RTOG trials in tumour sites that are subject to (large) respiratory motion are considered reliable when considering the motion management aspect of each used radiation technique. On top of that, also the PTCOG subcommittee on thoracic indications [PTCOG-thorax] has

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reported consensus guidelines on thoracic malignancies (Chang et al. 2017) and the RTOG subcommittee for lymphoma [PTCOG-lymphoma] has produced several reports on standardization of this indication for proton therapy (Aznar et al. 2021).

With the development of PBS systems, the impact of respiratory motion on the target volume and the therapeutic dose deterioration during scanning beam delivery were major concerns. The first research initiatives begun in early 2000s at PSI (Paul Scherrer Institute, Villigen, Switzerland) and GSI (GSI Helmholtz Centre, Darmstadt, Germany), which created an avalanche of research projects in several other institutes worldwide. In photon therapy, the same concerns related to interplay effects between tumour motion and treatment delivery were studied and solutions related to respiratory gating and tracking became available in the last 10-15 years. The cross talk between the photon and proton therapy centres in exchanging patient data and reporting the outcome of their research activities was very productive. **The AAPM TG 290 report was recently published and it sets a clear standard in motion management for particle therapy** (Li et al. 2022). TG290 risk analysis found that interplay effects could have a negative impact on the dose distribution and be difficult to detect after or during the treatment. It is recommended to use rescanning methodologies, i.e. a repetition of the beam delivery is at least three consecutive parts, to mitigate interplay effects, which is what most PT centres apply in clinical routine. A cut-off value is suggested to decide which patients need rescanning. Methods to evaluate interplay effects suggest accumulating the calculated dose from all respiratory phases of the 4DCT, if possible, synchronized with the treatment delivery. Although interplay evaluation tools are currently in-house developed, commercial solutions are underway.

Besides rescanning of the PBS delivery, a motion management that is also applied to particle therapy is respiratory gating. Respiratory gating is successfully applied in both photon and proton therapy. However, in proton therapy, the treatment delivery is more time demanding compared to state of the art IMRT arc technology in photon therapy. With the additional use of respiratory gating for mitigating target motion during breathing, treatment delivery times are further increasing. If several treatment rooms are connected to a cyclotron, it may cause a general delay and reduced patient throughput of the entire facility. With the introduction of research in flash dose rates[10], the use of non-flash ultra-high dose rates is gaining more interest for research purposes. Currently the rescanning methodology as a motion management technique is a compromise between effectiveness of mitigating breathing motion and maintaining an acceptable patient throughput. It is questionable if rescanning will maintain its position as a generally accepted motion mitigation technique in particle therapy as ultra-high dose rates make their entry on proton therapy systems.

With the development of MRgPT systems, potentially gated treatments would become a standard in PT. It is expected that 2D MRI cine imaging can be used to perform intrafraction monitoring with 4 seconds repetition rate (Hoffmann et al. 2020). Although the use of online cine MR images is

[10] Flash dose rates are doses of 50-100Gy which are delivered in very short time frames (< 1 second) and shown to be beneficial for significantly less healthy cell kill compared to large tumour cell kill, i.e. a significant increase in the therapeutic window between sparing of OARs and tumour control.

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potentially revolutionizing intrafraction imaging in PT, feasibility of cine imaging on a MRgPT system is not yet provided, majorly waiting for the physical realisation of a prototype MRgPT system.

4.4.3 Research needs

The goal of IGPT is to reproduce the patient anatomy observed at the time of simulation during each treatment session and otherwise minimize or mitigate any observed differences. The following items summarize the major research requirements:

1. The use of photon counting CT to reduce range uncertainty in PT and segmentation of metal implants and metal artefacts.
2. Development of online adaptive PT based on online-CBCT imaging. Although it is currently lacking in PT, major steps forward have been made in the last 5 years for photon therapy. It is important that IGPT catches-up towards IGRT solutions, i.e. application of (iterative or AI) scatter correction, AI to facilitate online re-planning, rapidness of CBCT acquisition as photon therapy evolves towards closed-bore solutions to increase gantry speed rotation. In the long run, online CBCT imaging of diagnostic image quality on proton therapy systems are required to support online adaptive PT on a large scale. For randomized clinical trials, levelling adaptive workflows would bring additional value to the comparison between photon and proton therapy.
3. Development of prototype MR-guided PT systems are needed to allow the investigation of online adaptive radiotherapy. It is currently not clear if online MR images, with deteriorated image quality compared to diagnostic MR imaging, allows to further reduce side effects in patients compared to an online CBCT-based adaptive workflow. Randomized clinical trials are needed to indicate if there is a return of investment for the development of MR-guided PT systems on a large clinical scale. Further research is also required for improving the uncertainty in dose calculations based on online MR images from MR-guided PT systems. In that context, research will majorly focus on the use of AI and a-priori knowledge from upfront diagnostic MR imaging.
4. Standard reports or guidelines on how to implement the simple first order IGPT approaches. A mix of different imaging modalities are available and each PT centre handles them according to their own situation. Weekly re-CT imaging of the patient in a simulation room (to enable efficient and effective adaptive PT) is the most preferred approach by PT centres because of the streamlined workflows that already exist. This shows the large gap that exists between proton treatment systems and full online adaptive photon therapy on the photon therapy side. In terms of reporting clinical outcomes for patients randomized between photon and proton therapy, it is evident that some bias is introduced resulting in a negative result for PT.
5. In the domain of IGPT and motion management a major research effort is needed in the development and clinical implementation of techniques on MR-guided PT systems, such as respiratory gating and tracking. Current MR-guided PT systems present technical limitations in the magnet design that supports the proton beam pass-through while supporting optimal image quality. It is expected that the quality and resolution of MR images will be considerably lower in comparison to the current MR-guided photon systems and the impact on motion

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management techniques from deteriorated online (1D or 2D) MR images is still subject of further research.

6. For motion management, the research from the last 20 years has proven to be effective and all clinical proton centres apply similar and effective methods such as rescanning and respiratory gating. It is still the question if better tools for interplay effects can be provided to clinical users (although commercially available software packages are underway). Additionally the realization of ultra-high dose rates on PT systems can still create a shift in motion management strategies towards full respiratory gating and this can be potentially improved with future MR-guided proton therapy systems.

4.5 Biological optimization of PT and the clinical value of RBE

4.5.1 Motivation

Protons can improve treatment conformity and reduce the amount of normal tissue exposed to significant doses of ionizing radiation, resulting in a reduction in adverse health effects, particularly for tumours near to critical and sensitive healthy tissues (Gondi, Yock, and Mehta 2016) . However, there are potential risks resulting from the greater uncertainties about the radiobiology of protons (Sorensen, 2021) compared with photons and whole-body scatter neutrons doses from proton delivery systems etc.

There are several important underlying biological factors responsible for an enhanced RBE of protons relative to photons. Even though per unit dose, protons induce the same number of DNA DSBs as photons, the distribution of the DSBs in the DNA, the local complexity of the DSBs and the properties of the DSBs signalling and repair mechanisms may differ between protons and photons and affect the RBE.

Proton therapy is currently planned and delivered based on a constant proton RBE relative to high-energy photons of 1.1, meaning that a given proton dose is expected to be equivalent to a 10% higher photon dose for tumours and normal tissues. There are number of variables such as beam delivery technique, dose, irradiated volume, proton energy, cell type, proportion of cancer stem cells in the tumour, tumour oxygenation level, intrinsic radiosensitivity, and the biological or clinical endpoints can add to complexity of the RBE measurement. Indeed, there are advantages of using a constant RBE in a clinical setting as converting photon doses into equivalent proton doses is easy and straightforward.

4.5.2 Status

The AAPM TG-256 on the Relative Biological Effectiveness of proton beams in radiation therapy published their report in 2019 (Paganetti et al. 2019) . The report outlines basic concepts of RBE, the biophysical interpretation and the corresponding mathematical formulations. It was concluded that the current clinical practice of using a constant RBE for protons should be maintained but it should be reconsidered in specific clinical situations. For that, there is the need to identify sites and treatment strategies where variable RBE might be safely employed. The group underlined the need for collecting clinical data of RBE doses and their correlation with clinical outcome. The report postulated the

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assessment of the potential clinical consequences of delivering biologically weighted doses based on LET and/or RBE as a function of dose and biological endpoints and the assessment of the potential for harm and benefits associated with the clinical implementation of variable RBE and LET models into TPS. The TG suggested that further experimental work is required for unravelling relationships among in vitro, in vivo, clinical RBE and for the development of recommendations to minimize the effects of uncertainties associated with RBE for well-defined tumour types and critical structures.

The paradigm of constant RBE protons is questioned by researchers (Tilly et al. 2005; Mohan et al. 2017) and by large associations/organisations, such as the ETPN. Notably, during the seventh EPTN workshop in 2021, a survey (Heuchel et al. 2022) showed that almost all European PT centres considered a variable proton RBE but did not necessarily apply it indicating that clinicians are aware of the RBE variation. Scientific evidence supports the RBE variation along the proton beam track considering all tissues where proton irradiation is used (Sorensen et al. 2021; Paganetti et al. 2019). The question becomes the extent and form, in which the proton RBE variation affects patient treatments.

It is also known the LET increases with depth along the spread-out Bragg peak (SOBP) with an increase at the distal-edge, which results in an increase of RBE. This effect along with the biological effects of scattered and secondary protons and neutrons at the distal edge add uncertainty to treatment planning. However, it is still unclear how they affect clinical outcome. Additionally, the position of the SOBP distal edge is critical and often coincides with healthy tissues and critical structures in the tumour vicinity, e.g. the optic nerve for brain tumours. This is an important issue particularly for paediatric patients, for whom PT is strongly recommended as a healthy tissue sparing method as most patients belong to long-term cancer survivor group.

There is an ongoing debate on the clinical effect of the increased RBE towards the distal edge and there is increasing awareness of clinical uncertainties in PT arising from RBE (Paganetti 2014). Most research on proton RBE is based on in vitro cell survival and the RBE of several endpoints, e.g. senescence, autophagy, oxidative stress, is not known. Few reports have described the effect of proton irradiation on primary stem cells survival and differentiation ability, which may be involved in development of severe late effects of PT. Most late radiotherapy effects, e.g. secondary cancer, tissue necrosis and vascular diseases, involve several biological mechanisms, including cell death, chronic inflammation, DNA repair. Moreover, RBE heterogeneity is present among cell lines (even for the same LET), which could be due to the cell genetic background and might affect the DNA repair capacity, damage signalling, cell cycle arrest, level of expressed antioxidant enzymes proliferation, resulting in increased sensitivity/resistance of the cells to PT. Finally, the extent to which the involved biological mechanisms are affected by a non-constant RBE value is still an open question.

4.5.3 Research needs

At this stage of discussion, it is still not possible to unequivocally conclude the clinical value of constant or varying RBE. In addition to analyses of clinical research, the following biological studies are considered:

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1- **In vitro mechanistic and novel cell experiments** to evaluate DNA repair capacity, DNA damage signalling, the levels of antioxidants, proliferation rates, induction of senescence, in cells exposed at the SOBP, beam entrance area as well as the distal end-edge of SOBP. Comparison of the effects at entrance, SOBP and distal end-edge will give us information about RBE at different locations on the proton track.

2- **Experimental evaluation of Physical quantities** such as the measurement of LET for commissioning, TPS validation and clinical evaluation. Such quantities can support biophysical models and prospective research.

3- **Studies by high-throughput screening methods on cancer cells and normal cells** exposed to protons, as above, are important to be performed. The analysis may focus on exploring the differential responses between the protons and photons at the levels of gene expression, protein expression, microRNA etc. It will be important to look as extracellular vesicles which are involved in cell-cell communication and non-targeted effects

4- **Multicentre databanking** from proton versus photon radiotherapy patients: there is a lack of databank with clinical and dosimetric data to follow up the outcome of PT versus photon in Europe. If such a database were available, we could have knowledge about how effective PT is in comparison with photon radiotherapy considering the treatment outcome. We could also explore the levels of severe healthy tissue effects induced by PT versus photon RT.

   Since 2019, an EC supported project is running and dealing with collection of dosimetric and medical data on paediatric proton therapy versus photon therapy patients (HARMONIC). Dosimetric data for OAR within the beam and outside the beam will be available. This is an excellent starting point but as the project is running for 5 years and most of severe late healthy tissue effects will be developed after 5 years, an economical support for continuation of the databanking will be needed and the databank might be opened for new collaborative projects.

5- **Multicentre biobanking** from proton versus photon radiotherapy patients: to understand the biological and long-term effects of proton versus photon radiotherapy a biobank from the radiotherapy patients will be important. The biobank could be set up engaging several radiotherapy clinics (proton and photon radiotherapy). The best scenario is to collect biosamples prospectively (collecting samples from each patient before, after finishing therapy, e.g. at the last fraction, and long-time after finishing the therapy, e.g. 1, 3 and 5 years after finishing therapy). The biosamples might be blood and saliva, which have been prepared to extract proteins, RNA, DNA, serum, plasma and other cellular compounds from. The extracted materials could be subjected to up-to-date and high-throughput screening analytical methods to find out the short as well as long-term changes that radiotherapy (photon/proton) induce in the patients and correlate them with clinical and dosimetric information from the databank concerning follow up outcomes (same patients).

   Today, a pilot study with 50 paediatric patients receiving PT and 50 receiving photon RT is ongoing within the HARMONIC project engaging five PT centres in Europe. This type of planned analyses will be important to explore the differences between the photon and proton irradiation and will give us information about the RBE of proton considering tumour as well as acute/late healthy tissue effects.

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4.6 Dosimetry of Pencil Scanning Beam - primary standard for pencil beam scanning (PBS) dosimetry

4.6.1 Motivation

Accurate radiation dosimetry is essential in radiation therapy of cancer patients as it ensures that the prescribed dose is truly delivered to the patient. One of the underlying principles for patient-specific dosimetry is based on the ICRU recommendation that the dose delivered to the planning target volume in the patient should be within -5% to +7% of the prescribed dose at the 95% confidence level (2σ) (ICRU 2007). These uncertainties are overall uncertainties and include dose delivery, dose measurements, and dose calculation uncertainties. Although the IAEA TRS-398 code of practice recognized this aim as unrealistic, in order to achieve such precision, an absorbed dose in water, determined in the reference conditions, should be performed within an uncertainty below 1% (1σ) (Andreo P et al. 2000; Karger et al. 2010).

The accuracy of radiation dosimetry depends on several factors, the central ones being the calibration of the dosimeters and the transfer of calibration from the standard conditions with good accuracy. Current practice in dosimetry is based on international codes of practice (Andreo P et al. 2000; ICRU 1998), that ensure dosimetric consistency between sites. Nevertheless, the codes of practice, implicitly the tools and the established metrology chain they imply are very much focused on conventional X-ray dosimetry. Thus, they recommend the calibration of detectors (usually ionization chambers) in terms of absorbed dose to water in a photon field, most commonly ^{60}Co photons. The calibration transfer is achieved using beam quality correction factors and chamber specific perturbation correction factors. This approach has provided satisfactory results for the dosimetry of photon beams, but it has higher associated uncertainties (≥2% (1σ)) for the dosimetry of proton beams. In addition, the experience of proton dosimetry, which has been used to design the mentioned codes of practice, was largely derived from the technology existing before their publication, employing passive scattering technology capable of irradiating broad proton fields. Developments in proton therapy technology have led to most treatments nowadays being delivered with PBS which provides both a better use of the proton beam and also the increased flexibility required for advanced modalities like intensity modulated treatments. Consequently, present standards and protocols for the dosimetry of protons (and implicitly of other ions) are regarded as inadequate for modern technologies as they increase the uncertainties in the dosimetry chains. This in turn has the potential to jeopardise the advantages of proton treatments and could increase the challenges for inter-comparison between institutions, an essential point for the preparation and quality assurance of clinical trials. From this perspective, the needs of the dosimetry of proton PBS reside in the establishment of primary standards for proton pencil beams, characterisation of suitable detectors to be used in proton beams and the development of a robust framework for the transfer of calibration for dose quantification delivered by complex beams. These will contribute towards improving the inter-comparison between European and international proton therapy centres.

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4.6.2 Status

The European Commission's report No. 162 (EU 2013) proposing criteria for acceptability of medical radiological equipment used in diagnostic radiology, nuclear medicine, and radiotherapy recommends that the equipment used for radiation therapy "must be well maintained, regularly calibrated and traceable (where appropriate) to national standard laboratories." This highlights the need for both good calibration standards as well as the traceability of measurements from the standards laboratory to the user. Nevertheless, a dosimetry standard for protons is currently lacking necessitating dosimetric traceability to other beam modalities, such as Co-60 photons, at the cost of additional uncertainty compared to photon dosimetry. In addition, present codes of practice (Andreo P et al. 2000), recommend the use of broad passively scattered modulated proton beams for reference dosimetry and reflect the treatment technology available at the time of their publication, based on weighted fields with spread-out Bragg peaks (SOBP). Modern proton treatments however are performed with broad beams created from the superposition of equidistant pencil beams of various energies. This technology has rapidly proliferated in recent years and many passive scattering installations have been converted to active scanning as the technology has become the current standard of clinical practice. For active scanning beams, the beam monitor chamber is calibrated for each nominal beam energy separately (Palmans and Vatnitsky 2016) and in each such case, the broad reference beams consist of equidistant pencil beams of equal nominal energy and an equal number of monitor units per beam. The differences between current clinical practice and recommendations of the existing codes of practice represent additional aspects that increase the uncertainties in the dosimetry chain for proton pencil beam scanning. From this perspective, the development of a robust framework for traceable measurements in proton beams is highly needed.

Mainly four techniques are used as primary dosimetry methods for light-ion beams (protons, carbons): calorimetry, fluence measurements, chemical dosimetry, and ionisation chamber (IC) dosimetry. The simplest method used for the fluence determination is using a Faraday cup (FC). The most relevant features of the FC devices include its very simple design, dose-rate independency (interesting for high dose-rate beams considerably most important in case of new modalities like FLASH), and beam quality independence (pulsed, continuous, scatter, or scanned techniques). Several comparisons of the FC dosimetry with calorimetry and IC dosimetry have been described in the literature (Verhey et al. 1979; Kacperek and Bonnet 1989; Grusell et al. 1995; Cambria et al. 1997; Delacroix et al. 1997; Jones et al. 1999; Cuttone et al. 1999; Newhauser, Burns, and Smith 2002; Goma, Andreo, and Sempau 2013), in general yielding an agreement within a couple of percent with other methods, but on some occasions disagreement of 5-10% were demonstrated. For this reason, FC dosimetry became less and less recognized as a valuable primary method.

On the other hand, the calorimetry is the most direct way to measure absorbed dose. It is based on the measurement of the temperature rise of a given volume element of this instrument when it is exposed to a source of radiation. The graphite and water calorimeters are used as the basis for references of absorbed dose in water, which is the reference medium for radiotherapy. Indeed, water and graphite are close to biological tissues because of their composition or atomic number. Several studies have reported the use of calorimeter in proton beams (Verhey et al. 1979; Schulz et al. 1992;

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Siebers et al. 1995; Palmans et al. 1996; Delacroix et al. 1997; Gagnebin et al. 2010; Palmans et al. 2004; Medin 2010; Renaud et al. 2016; Christensen, Vestergaard, and Andersen 2020). However, a calibration service based on the primary standard calorimeter in the proton beam does not exist. In order to address the absence of an operational primary dosimetric standard, the potential of calorimeters as primary measurement standards for proton beams has been investigated as they provide a direct way to measure an absorbed dose. The National Physics Laboratory (NPL, Teddington, UK), the UK's national measurement institute, has proposed a graphite calorimeter as a Primary Standard Proton Calorimeter taking advantage of the graphite sensitivity compared to water (a temperature rise in graphite six times higher than in water is expected) and its thermal diffusivity (as the heat dissipates quicker in graphite, more measurements can be performed within a given time interval (Lourenco et al. 2022). Nevertheless, these attempts address a limited range of specific reference conditions, and the systems need validation in the increasingly complex radiation fields that are nowadays used clinically.

An important aspect that needs to be addressed is the time structure of dose deposition, with rather high instantaneous energy deposition in the scanned fields, and not in the least the impact of the pulse structure of the proton beam that may depend on the performance and functioning of the accelerator. These are important aspects to consider in defining a primary standard for proton beams as well as in defining the perturbation correction factors for the transfer of calibration.

The application of an extrapolation chamber as a primary dosimetry instrument in a 250 MeV non-modulated proton beam was described by Zankowski (Zankowski et al. 1998). The authors have found that agreement with Farmer type IC was within 5%.

The performance of chemical detectors, like alanine detectors considered, for reference dosimetry also has to be characterised and validated in scanned proton beams. Indeed, Alanine-based dose determinations in proton beams have been shown to lead to a systematic deviation of about 2% compared to ionization chamber dosimetry in water and plastic materials (Carlino et al. 2018), although a more recent study reported good agreement with ionisation chambers (Carlino et al. 2021).

With respect to ionisation chamber dosimetry, efforts have been made for the adaptation of the recommendations in the current code of practice to the features of modern proton therapy beams. Palmans et al. (Palmans et al. 2022)have recently reviewed the current knowledge on the beam quality correction factors for reference dosimetry of clinical proton beams. They proposed that changes are needed from the previous edition of the TRS 398 code of practice (Andreo P et al. 2000), especially for cylindrical ionisation chambers and less for plane-parallel ionisation chambers, further highlighting the uncertainties associated with the use of that code of practice. They also reported that the overall relative standard uncertainty (k=1) for the new beam quality correction factors was estimated to be 1.4%.

Emerging developments in proton therapy such as the increased availability of ultra-high dose rates or FLASH radiotherapy further increase the challenges for dosimetric accuracy and open new avenues for future research for the dosimetry of proton beams.

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4.6.3 Research needs

Dosimetry is a well-established and mature branch of medical physics and metrology. Despite of that in the field of proton therapy an additional research and an investment in metrology are needed to assure safe dosimetry of Pencil Scanning Beams and in FLASH therapy:

(i) establishment in Europe primary standards for proton beam, in particular Pencil Scanning Beam, and proton beam dosimetry

(ii) development of suitable detectors to be used in proton beams, including detectors suitable for characterising the radiation quality of the proton beams by accounting for variations in energy depositions along a proton track and especially towards the end of its range, as well as in beams with mixed quality as might result in modern complex fields created from the superposition of plateaus and Bragg peaks of individual pencil beams.

(iii) establishment of the machine-specific reference fields for the transfer of the dosimetry standards and a framework for the transfer of calibration for dose quantification (also delivered by complex beams) to Secondary Standards Dosimetry Laboratories and finally to clinics. It will also cover improvement in material and tissue characterisation required for the transfer of calibration from standard reference conditions to those conditions that may be encountered clinically.

(iv) development of tools and methodology for dose determination from the complex beams. This includes detector improvement and characterisation, e.g., on handling ion recombination effect or handling of increased energy deposition density. Additional studies concern the investigation of the influence of beam structure and the temporal aspects of dose deposition in scanned proton beams.

4.7 Out of field doses and the risk of secondary cancer

4.7.1 Motivation

The induction of second cancers from radiotherapy is a growing concern in cancer survivors and especially for children and young adults having a long life expectancy after their treatment. This is particularly relevant for the EU where about 2.5 new million cases of cancer are diagnosed each year and where radiation is employed in the management of the disease in about half of the cancer patients. This has made cancer diagnosis no longer a death sentence, but a survivable disease for many patients. Experience from the survivors of photon therapy has shown that up to 20% of patients develop second malignancies, but only about 5% of these tumours can be attributed to radiation therapy

Modern radiotherapy techniques are able to precisely deliver the required dose to the treatment volume. Highly conformal photon plans employing intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) and tomotherapy (TT) are able to fulfill most of the dose constraints for critical organs but for the price of irradiating a large volume of healthy tissue. Since the irradiation is performed from many directions, a large fraction of the body is irradiated with primary beams, which may lead to doses in the range of grays and tens of grays for a considerable volume of the body. Despite the fact that such doses are lower than the dose constraints for particular organs and tissues, they guarantee only the lack of deterministic effects, but non-deterministic effects are still

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a concern. In modern proton therapy (PT) narrow proton Pencil Scanning Beams (PBS) deposit maximum energy at the end of their range, depending on the energy of the beam. Due to the Bragg peak phenomena the entrance dose is reduced and the exit dose practically eliminated. Thus, the unnecessary dose in the healthy tissue is greatly reduced. In addition to the direct exposure of the primary beam, healthy tissue is also irradiated by the scattered and secondary radiation, such as ions, electrons, neutrons and photons produced, in interactions with beam forming elements, immobilization system and the patient body. In particular neutrons with high biological effectiveness were considered as potentially dangerous for induction of secondary tumours (Hall 2006).

Nowadays survival and quality of life (complications, early side effects) are the two end-points of cancer treatment. In spite of a broad amount of computational, experimental and clinical data, the optimization of the risk of complications, in particular secondary cancers, is not in the mainstream of clinical protocols. There is a general consensus on the need to reduce unnecessary exposure of healthy tissue for young survivors, but no common understanding how the knowledge on secondary cancer risk should be applied in clinical practice.

4.7.2 Status

A broad discussion on the secondary cancers in proton therapy started after the debate on the possible adverse effect of neutrons generated in passive scattered beams. IMRT became a clinical standard which increased the fraction of healthy tissue irradiated with primary beams. In the last decade several review papers and reports were published on unwanted exposure in radiotherapy and the corresponding risk of secondary cancer (Kry et al. 2017; Newhauser and Durante 2011; Romero-Exposito, Toma-Dasu, and Dasu 2022).

Task Group 158 of the AAPM published in 2017 a comprehensive report on the **radiation doses outside the treated volume from external-beam radiation therapy** (Kry et al. 2017). The report was designed to provide guidance for medical physicists who may have limited experience with measuring, calculating, reducing, and reporting non-target doses. In particular, the report " … (a) highlights major concerns with non-target radiation; (b) provides a rough estimate of doses associated with different treatment approaches in clinical practice; (c) discusses the use of dosimeters for measuring photon, electron, and neutron doses; (d) discusses the use of calculation techniques for dosimetric evaluations; (e) highlights techniques that may be considered for reducing non-target doses; (f) discusses dose reporting; and (g) makes recommendations for both clinical and research practice." Notably, the report includes sections dedicated to the doses and risks from proton therapy and it discusses the non-target doses, i.e. doses outside the planning target volume, PTV, which takes into account doses from both primary and secondary radiations. As an end point, not only the risk of secondary cancers is considered, but also cardiac toxicity, foetal doses, implantable pacemakers, cataracts and skin reactions. An important part of the report is the guidance on how to minimize the nontarget exposure at the treatment planning level and during the irradiation. This report can be used to assess dose ranges which are expected from different treatment modalities and to design treatments to minimize non-target doses.

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The out of field doses and the risk of secondary cancer of young patients treated with protons was discussed in detail by Romero-Exposito et al. (Romero-Exposito, Toma-Dasu, and Dasu 2022). For the two most common indications for PT in children (brain and craniospinal tumours), the treatment with passively scattered proton beams may lead to equivalent doses in organs of up to 200 mSv and up to 900 mSv respectively. Application of the scanning beam reduces the unnecessary exposure by approximately one order of magnitude with a spread ranging from 2 to 50 times. For assessing the risks, several factors must be taken into account e.g. size of child (for small child organs closer to target volume), age (sensitivity decreases with age), higher sensitivity of women (breasts). Despite a quick development of Monte Carlo calculations, sometimes referred to as gold standards, the paper underlines the usefulness of existing analytical risk models, which can be easily implemented into TPS. Since the most results are coming from passively scattered proton beams, further investigations are warranted for scanned-beam delivery systems.

The summary of **late-effects after radiotherapy with advanced technology treatment** was provided in the review paper (Newhauser and Durante 2011). Modern protons and photon beams should theoretically lead to better outcomes but these improvements are not easily quantified. It is pointed out that the number of incident cancers and long-term cancer survivors is expected to increase substantially but the evidence from controlled clinical trials and epidemiology studies are lacking. The paper reviews several key research methods of relevance to late effects after advanced technology proton-beam and photon-beam radiotherapy, such as determination of exposures to therapeutic and stray radiation, advances in exposure calculation methods, uncertainties, *in silico* studies, computing infrastructure, electronic medical, records, and risk visualization.

Indispensable data for verification of analytical models and results of Monte Carlo calculations on out of target dose are coming from in phantom experiments, in particular with anthropomorphic phantoms. Huge experimental data come from the extensive experiments performed at Trento, Kraków and Maastricht proton therapy centres by the Working Group 9 of the European Radiation Dosimetry group EURADOS (Stolarczyk et al. 2011; Farah et al. 2014; Farah et al. 2015; Mojzeszek et al. 2017; Mares et al. 2016; Stolarczyk et al. 2018; Knezevic et al. 2018; De Saint-Hubert et al. 2018; Wochnik et al. 2021; Majer et al. 2022; Van Hoey et al. 2022; Mares et al. 2022). All experiments were supported by detailed Monte Carlo transport calculations. Results confirm that the out of target doses in proton therapy using Pencil Beam Scanning technology are up to 1-2 orders of magnitude lower than the corresponding doses in conventional photon beams. One of the difficulties in comparison of experimental photon and neutron data was the inadequacy of dosimetric quantities used in radiation protection, such as dose equivalent, equivalent dose, effective dose to evaluate risk of secondary cancers in radiation therapy.

4.7.3 Research needs

Several research problems of relevance for better determination of unwanted exposure and in consequence, the late effects in proton therapy, were formulated along the years (Newhauser and Durante 2011; Sanchez-Nieto et al. 2022). It was thus postulated:

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(i) to develop and experimentally verify algorithms to calculate exposures to tissues outside the treatment field. The algorithms should consider all major scattered and secondary radiation, including neutrons;

(ii) to develop primary and secondary reference fields of high-energy neutrons for calibration of instruments in realistic radiation fields and in consequence to measure correctly the exposure;

(iii) to improve methods to reproducibly and consistently determine radiation quality, because of the growing interest on the dependence of biological effectiveness on proton energy (LET);

(iv) to develop methods (procedures) to accumulate exposures from therapeutic and imaging procedures;

(v) to develop tools for risk visualization, analysis, communication, and documentation; and finally

(vi) to prepare algorithmic methods to support decision making in avoiding non-essential radiation risks.

One of the conceptual problems by evaluation of integrated risk is the lack of risk coefficients at different dose levels and from different radiation qualities. The radiation weighting factors or Quality Factors applied in radiation protection cannot be directly applied to risk models, in particular for mixed radiation fields. Dedicated research is needed to propose the relevant dosimetric quantities and to derive from clinical data the corresponding risk coefficients and their uncertainties.

The research on the relevant dosimetric quantities to assess risk after the unwanted exposure in radiotherapy requires multidisciplinary metrology approach i.e. clinical, radiobiological and physical data. This analysis should be complemented by selection of the most appropriate risk model, which considers non-linearity of the dose-response relationship for high radiation doses.

The preparation of an algorithmic approach to include out of target doses in decision making is warranted and biological index performance has been proposed based on data from Treatment Planning Systems (Sanchez-Nieto et al. 2019). Such developments can be considered from the perspective of the experience of model-based selection developed by Langendijk and co-workers (Langendijk et al. 2013; Langendijk et al. 2021).

The need for experimental determination of radiation quality (LET) of the therapeutic proton beams is broadly discussed but not yet required by international regulations. Nevertheless, the need for harmonisation in reporting radiation quality for proton therapy has been demonstrated (Hahn et al. 2022) and will be needed to ultimately provide recommendations in this field.

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5 Summary and Conclusions

Modern proton therapy treatment units with scanning beams offer a substantial advantage over the conventional photon therapy because of significant reductions in normal tissue doses. Despite many technical, financial and organizational difficulties the perspectives of further development of proton therapy are promising.

In the time of the fast growth of proton therapy (PT), in particular due to substantial technological progress, international guidelines and recommendations are essential for standardization of procedures and safety of patients. Proton therapy recommendations in the field of dosimetry and medical physics issued by ICRU, AAPM and IAEA are well recognized and broadly accepted in medical physics and dosimetry. New reports are in preparation to update the recommendations for the new generation of treatment techniques, in particular for scanning beams. The annual PTCOG conference, gathering more than 1000 registered participants, is considered as the most important scientific meeting in PT worldwide. In Europe, the collaborative approach proposed by EPTN has a good chance to harmonize the patient treatment and to deliver valuable data for evidence-based medicine.

The main barrier for the further growth of proton therapy remains the high price of investment and operation and more clear patient-oriented clinical advantages as compared to conventional methods for a wide range of applications. More research is needed to reduce the price of the accelerators and to achieve technical capabilities equivalent to those available in classical radiotherapy e.g. in terms of image guidance. First clinical results obtained with a high-dose-rate (FLASH) of electron beams for shallow skin tumours are very promising and stimulated corresponding research in PT. Reproducibility of the FLASH treatment, biological response, the possibility to apply to deep seated tumours and to introduction of FLASH into the overall care matrix of a patient should be studied. Image guidance and the corresponding motion management is an unsolved problem in PT and requires major research to catch-up conventional therapy. Biological optimization of PT and the clinical value of RBE is currently a hot topic. Better understanding of this issue should be brought by dedicated biological research, including *in vitro* mechanistic and novel cell experiments, studies on cancer cells and normal cells exposed to protons, multicentre databanking from proton versus photons and multicentre biobanking to understand the biological and long-term effects of proton. There are no primary standards for proton beams and the corresponding dosimetry in Europe. In addition, establishment of the machine-specific reference fields for the transfer of the dosimetry standards will improve the status of clinical dosimetry. It is also not clear how to support decision making in avoiding non-essential radiation risks due to out of target (field) doses.

The most urgent issue is to consolidate clinical research to show in which cases proton therapy demonstrates clinical advantages over conventional techniques. Some indications are already internationally accepted, such as tumours of the Central Nervous System (CNS), eye melanoma and solid tumours by children and young adults. For others, conduction of randomized controlled studies in PT undoubtedly requires an international network e.g. as proposed by the European Particle Therapy Network (EPTN) and the Proton Therapy Cooperative Group (PTCOG). For tumours with low incidence

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collection of prospective data in international databases should be encouraged. European efforts to increase PT capacity should be coordinated and integrated in European-wide clinical studies, setting up a minimum level of data and quality management requirements to make the clinical studies interoperable and robust.

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6 Appendix

6.1 A partial list of EU funded projects supporting research in proton therapy:

ARDENT (Advanced instrumentation to monitor radiation dose), 3.9M€;

BARB (Biomedical Applications of Radioactive ion Beams), 2.5M;

Cardio-kit (A disruptive medical device to enable proton therapy as non-invasive and automated treatment of heart arrhythmias), 2.5M€;

ENVISION (European NoVel Imaging Systems for ION therapy), 6M€;

EUCARD-2 (Enhanced European Coordination for Accelerator Research & Development), 8 M€;

HIL (ultra-compact high-performance proton therapy system), 2.4M€;

HIPPOCRATE (Hybrid Imaging of PET and PrOmpt gamma for preCision RAnge- and biological- guidance in proton ThErapy), 170k€;

iMPACT (innovative Medical Protons Achromatic Calorimeter and Tracker), 1.8M€;

INSPIRE (transnational access to research capabilities employing proton beams at clinical energies), 5M€;

LPT (Laser based Proton Therapy), 2.7M€;

OMA (Optimization of Medical Accelerators), 3.9M€;

PROTECT (Proton versus Photon Therapy for Esophageal Cancer - a Trimodality Strategy), 1.5M; Proton CT reconstruction with a Cone Beam CT prior 185k€;

PROTONMBRT (combination of protons for RT, sub-millimetre field sizes and a spatial fractionation of the dose), 2M€;

PROTONMBRT (Spatial fractionation of the dose in proton therapy: a novel therapeutic approach), 2M€,

PROTONSPOTSCANMET (Improving physical dosimetry and developing biologically-relevant metrology for spot-scanned proton therapy beams), 250k€.

SIRMIO (Small animal proton Irradiator for Research in Molecular Image-guided radiation-Oncology), 1.5M€;

ULICE (Union of Light-Ion Centres in Europe), 8.4M€;

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6.2 Overview of techniques for range prediction and its validation

Overview of techniques for range prediction and its validation. DECT, dual-energy CT; HLUT, Hounsfield look-up table; SECT, single-energy CT; SPR, stopping-power ratio. The TRL definition is according to the Horizon 2020 programme. Global verification accuracy of average range shifts within a field only. If subsequently an additional adaptation of the range prediction would be applied, e.g. HLUT refinement, this would bear additional uncertainties - for example an overestimation in one tissue together with an underestimation in another tissue could still exist, even if the integral range shift is minimized on average. Note that both techniques are able to validate an existing range prediction, however cannot replace the (voxel-wise) range prediction. Adapted from (Wohlfahrt and Richter 2020)

	Applicable for pre-treatment SPR prediction	**Applicable for SPR re-assessment during treatment**	**Technical readiness level****	**Current estimated range uncertainty**	**Advantages**	**Limitations**
SECT-based HLUT	2	In-room-CT/additional CT outside of treatment room	9	3-3.5 %		
DECT-based DirectSPR	2		8	≤ 2 %	Consideration of patient variabilities Currently highest accuracy level	No broad clinical experience yet
Photon-counting CT	2		6	2%	Superior detector technology	Systems not mature yet. No clinical realistic evaluation
Proton CT	2	2	4-6	?	Most direct determination	Not yet clinically implemented First systems only for head geometries Severe ring and streak artifacts
MRI-only SPR prediction	2	2	6	> 2 %	Superior tissue classification due to superior soft tissue contrast	Less quantitative image information Difficult differentiation between bone and air Interpatient variation in bone considerable
Range probes	0	2	6	1 mm^3	Also direct determination Easy to implement	Only single spots in treatment volume Information mixed with anatomy distal of treatment volume

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Prompt-γ-based range assessment	0	2	7	1.5 mm^3	No extra dose or time needed for acquisition Additional recognition of severe anatomical changes	Accumulation of information from multiple spots needed for better counting statistics

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