ESTRO

# Report on the ninth annual meeting and workshops of the European Particle Therapy Network

The European Particle Therapy Network (EPTN) was established in 2015 and became a task force of ESTRO in 2017 in response to the increase in the number of European particle therapy centres. The EPTN held its ninth annual meeting and workshops from the 26-27 October in Manchester, UK. The meeting was held in the Christie Centre in Manchester, and we wish to extend our sincere appreciation to our hosts. We are also grateful for the support of UK Research and Innovation's Science and Technology Facilities Council Advanced Radiotherapy Network+ (ARN+) for the workshops. We were pleased to see a strong resurgence of participants after the COVID-19 pandemic, with 70 participants from 15 European countries.

The network continues to grow, and publications, events and workshops organised by the Work Packages (WPs) are all thriving. Three workshops were organised for the day prior to the annual meeting, which were entitled Adaptive Proton Therapy, Evidence-based Proton Therapy, and Beyond Physical Dose. These workshops were reported on and discussed at the annual meeting. We were excited to see the focus during this meeting placed on the future organisation and role of the EPTN in being fully integrated into the world of radiation oncology, and on the reorganisation and expansion of its WPs, membership, and engagements.

WP6 (radiobiology) has decided to restructure to ease internal processes. Future activities will be split into task groups, each led by a WP member: clinical radiobiological effectiveness (RBE) will be led by Armin Lühr (Dortmund, Germany); experimental particle radiobiology by Briita Singers Sørensen (Aarhus, Denmark); education by Manjit Dosanjh (CERN); modelling by Bleddyn Jones (Oxford, UK); and particle FLASH radiobiology by Jörg Pawelke (Dresden, Germany). Professors Lühr and Sørensen will act as WP coordinators.

Following discussions within the network, it has been agreed to establish a new WP (8), which will be dedicated to setting up a data registry. This WP will be led by Esther Troost (Dresden, Germany) and Vincent Grégoire (Lyon, France).

The EPTN WPs are listed below:

| WP | Coordinators |
|---|---|
| 1. Clinical evidence | Hans Langendijk<br>Karin Haustermans |
| 2. Quality assurance | Oliver Jäkel<br>Sairos Safai<br>Stefano Lorentini |
| 3. Education | Morten Høyer |

| | |
|---|---|
| | Marco Schwarz<br>Rita Simoes |
| 4. Image guidance | Aswin Hoffmann<br>Alessandra Bolsi |
| 5. Treatment planning | Christian Richter<br>Tony Lomax |
| 6. Radiobiology | Brita Sørensen<br>Armin Lühr |
| 7. Health economy – HTA | Yolande Lievens |
| 8. Data registry infrastructure | Esther Troost<br>Vincent Gregoire |

## European particle therapy centres

No new particle therapy centres opened in 2022 or 2023 in Europe. In the UK, operations were discontinued in the Rutherford centres. Looking forward, several new proton therapy centres are expected to open within Europe in the next year: in the cities of Milan and Pavia in Italy, Oslo and Bergen in Norway, and Coruña, Barcelona, Bizkaia, Madrid, Malaga, Seville, Valencia, and Gran Canaria in Spain.

## EPTN-related events 2023 and 2024

Some of the principal events that took place last year or are planned for this year are:

- FLASH Radiotherapy and Particle Therapy: 5–7 December 2023, Toronto, Canada
- 2nd EPTN-ESTRO School Workshop: 30 November-1 December 2023, Groningen, The Netherlands
- PSI Winter School 2024: 14-19 January 2024, Villingen, Germany
- ESTRO School – Particle Therapy: 10-14 March 2024, Barcelona, Spain
- ESTRO 2024 Congress: 3-7 May 2024, Glasgow, UK
- Particle Therapy Co-Operative Group 62, 10-15 June 2024, Singapore

For a few years, radiotherapy has been integrated into the work of the EPTN, particularly in connection to WP3 – education. Due to the busy activity since the integration of radiotherapy, an EPTN workshop dedicated to it is planned for 2024. In addition, each WP organises multiple internal meetings, both virtually and physically, throughout the year.

## EPTN publications 2022 and 2023

Seven articles relevant to the EPTN were published in 2022 and 2023.

Di Perri D, Hofstede D, Postma A, Zegers CML, In't Ven L, Hoebers F, van Elmpt W, Verheesen L, Beurskens H, Troost EGC, Compter I, Eekers DBP. Development of explanatory movies for the delineation of new organs at risk in neuro-oncology. Clin Transl Radiat Oncol. 2022 Feb 15;33:112-114. doi: 10.1016/j.ctro.2022.02.005. PMID: 35243021; PMCID: PMC8857542.

Vaassen F, Zegers CML, Hofstede D, Wubbels M, Beurskens H, Verheesen L, Canters R, Looney P, Battye M, Gooding MJ, Compter I, Eekers DBP, van Elmpt W. Geometric and dosimetric analysis of CT- and MR-based automatic contouring for the EPTN contouring atlas in neuro-oncology. Phys Med. 2023 Oct 7;114:103156. doi: 10.1016/j.ejmp.2023.103156. Epub ahead of print. PMID: 37813050.

Crouzen JA, Petoukhova AL, Wiggenraad RGJ, Hutschemaekers S, Gadellaa-van Hooijdonk CGM, van der Voort van Zyp NCMG, Mast ME, Zindler JD. Development and evaluation of an automated EPTN-consensus based organ at risk atlas in the brain on MRI. Radiother Oncol. 2022 Aug;173:262-268. doi: 10.1016/j.radonc.2022.06.004. Epub 2022 Jun 15. PMID: 35714807.

Barcellini A, Massaro M, Dal Mas F, Langendijk JA, Høyer M, Calugaru V, Haustermans K, Timmermann B, Thariat J, Scartoni D, Vennarini S, Georg P, Orlandi E. A year of pandemic for European particle radiotherapy: A survey on behalf of EPTN working group. Clin Transl Radiat Oncol. 2022 Feb 24;34:1-6. doi: 10.1016/j.ctro.2022.02.004. PMID: 35243028; PMCID: PMC8885798.

Heuchel L, Hahn C, Pawelke J, Sørensen BS, Dosanjh M, Lühr A. Clinical use and future requirements of relative biological effectiveness: Survey among all European proton therapy centres Radiother Oncol 2022; 172, P134-139, July 01, 2022. https://doi.org/10.1016/j.radonc.2022.05.015

Knopf AC, Czerska K, Fracchiolla F, Graeff C, Molinelli S, Rinaldi I, Rucincki A, Sterpin E, Stützer K, Trnkova P, Zhang Y, Chang JY, Giap H, Liu W, Schild SE, Simone CB 2nd, Lomax AJ, Meijers A. Clinical necessity of multi-image based (4DMIB) optimization for targets affected by respiratory motion and treated with scanned particle therapy - A comprehensive review. Radiother Oncol. 2022 Apr;169:77-85. doi: 10.1016/j.radonc.2022.02.018. Epub 2022 Feb 18. PMID: 35189152.

De Roeck L, van der Weide HL, Eekers DBP, Kramer MC, Alapetite C, Blomstrand M, Burnet NG, Calugaru V, Coremans IEM, Di Perri D, Harrabi S, Iannalfi A, Klaver YLB, Langendijk JA, Romero AM, Paulsen F, Roelofs E, de Ruysscher D, Timmermann B, Vitek P, Weber DC, Whitfield GA, Nyström PW, Zindler J, Troost EGC, Lambrecht M; work package 1 of the taskforce "European Particle Therapy Network" of ESTRO. The European Particle Therapy Network (EPTN) consensus on the follow-up of adult patients with brain and skull base tumours treated with photon or proton irradiation. Radiother Oncol. 2022

## Call for papers – virtual special issue on automation in radiation oncology

A joint collaboration by two ESTRO journals, the Green Journal (radiotherapy and oncology) and phiRO (physics and imaging in radiation therapy), on automation in radiation oncology will soon be announced. The journals encourage the submission of manuscripts of novel studies that demonstrate clinical potential or applicability. In this virtual special issue, the papers will be presented under one umbrella, in order for parties interested in automation to find all relevant papers in one place. The deadline for submissions is 30 April 2024.

## The European Investment Bank and the European Union Directorate-General Santé

The European Investment Bank (EIB) has formerly financed hadron/proton therapy projects. Since 2018, the EIB has received many requests to finance new centres, which have been the subject of discussion with the EPTN. A proton therapy sub-group was created to develop a European perspective on accessibility, affordability, evidence, and distribution within the proton therapy sector. In its first meeting in 2018, the EIB decided to update the 2006 and 2011 clinical evidence studies. Following the COVID-19 pandemic, the 2020 report on the clinical evidence study showed the need for a European Union (EU) proton therapy registry, improved data sharing, and research and development (R&D) collaboration among centres. It concluded that there were lingering uncertainties and a lack of data regarding clinical evidence. Consequently, the EIB decided to pause further investment in proton therapy centres. A new study on the mapping of centres, R&D activities and the impact of COVID-19 commenced in 2022 with exchanges with the EU Directorate-General (DG) for Health and Food Safety (DG Santé) and the DG for Research and Innovation, and collaterally with the EPTN. Following continued contact between the EIB and EPTN, a formalised network to help bridge the knowledge gap along with a

database/registry was deemed crucial. Therefore, a new WP on the data registry has been established with the EPTN.

You can read about the activities of the EPTN, its WP structure and members, as well as announcements, publications, and previous reports, on the ESTRO-EPTN webpage ESTRO - EPTN.

**EPTN annual meeting,** Christie Centre, Manchester 2023

## Collaborative projects

### HITRI+

Sandro Rossi

The status of the project on heavy ion therapy research integration plus (HITRI+) (https://hitriplus.eu/) was presented by the project coordinator Sandro Rossi from the Italian Centre for Oncological Hadron Therapy (CNAO). This research infrastructure project is led by a consortium of 22 institutes from 14 European countries and brings together for the first time the four European heavy ion radiotherapy centres with major industries, universities and research laboratories. Prof Rossi said that the project had turned the halfway point. The networking activities (pillar coordinator Manjit Dosanjh) that have been performed so far were presented, with emphasis on communication and dissemination activities through online seminars and social media; the success of master classes and specialised courses; the significance of clinical networking to foster collaboration within the European clinical carbon ion radiotherapy field; and the crucial role of WP4 in the devising and implementation of a roadmap for the industrialisation of HITRI+ technologies. The joint research activities (pillar coordinator Maurizio Vretenar) have achieved important goals in terms of improving and upgrading the systems that are already in use at European facilities as well as providing the basic components of a future, next-generation design, to become the basis for future ion therapy centres. The transnational access section (pillar coordinator Marco Durante), which joins the research programmes of the four European ion therapy centres and links them to the GSI laboratory's work on biophysics research with ions, is the key pillar of the project. So far, besides the hours of beam time that have been devoted to external research groups, 18 clinical researchers from 10 countries have taken advantage of the opportunity to participate in clinical research on hadron treatment through clinical research access. They were able to compare treatment plans and to discuss the carbon-ion eligibility of

clinical cases and for clinical research trials in hadron therapy, to participate in the workflow of hadron treatment.

## EU-MSCA-ITN RAPTOR project

Francesca Albertini

The EU-Marie Skłodowska-Curie Actions-Innovative Training Networks real-time adaptive particle therapy of cancer (RAPTOR) project, supported by a €4 million fund, is a collaborative effort that involves 15 PhD students from institutes in Europe. They are united by the common goal of advancing online adaptive particle therapy to improve patient outcomes. Divided into six distinct WPs, the project addresses challenges through three scientific WPs that focus on aspects of the adaptive workflow: imaging, intervention and verification.

WP3-imaging, led by Chiara Paganelli at POLIMI in Milan, Italy, is designed to provide on-board volumetric image guidance that is suitable for daily and potentially real-time adaptive proton therapy planning. WP4-intervention, led by Stine Korreman at Aarhus University, Denmark, is aimed to refine planning procedures through the development of automated treatment plan optimisation coupled with efficient clinical approval strategies. WP5-verification, coordinated by Christian Richter of OncoRay in Dresden, Germany, aims to develop, evaluate and translate methods for independent verification of the delivery of adapted treatment plans throughout the online adaptive loop.

The scientific work packages are complemented by three additional components. WP1-education, led by Katia Parodi at Ludwig Maximilian University in Munich, Germany, fosters a creative research environment for interdisciplinary and intersectoral education. WP5-dissemination, coordinated by Kristjan Anderle from Cosylab Ljubljana, Slovenia, is focused on the promotion of the impact and significance of RAPTOR project contributions in the field of cancer research. The overall project coordination, encapsulated in WP6 management, is overseen by Dr Francesca Albertini from PSI, Switzerland.

The project is halfway through; it started in March 2021 and is scheduled to end in September 2025. It has achieved all planned deliverables and milestones and received a positive mid-term evaluation. Three schools, open not only to RAPTOR students but also to external participants, have been held to train a new generation of students in particle adaptive therapy. The 15 RAPTOR PhD students have also made good progress in their projects, resulting in good participation in national and international conferences and the publication of 11 papers in peer-reviewed journals.

Detailed information and progress plans can be found on the official RAPTOR website (https://raptor-consortium.com/) (https://www.linkedin.com/company/72771602/).

### PROTECT-

Cai Grau, Denmark

The proton versus photon therapy in the treatment of oesophageal cancer (PROTECT) project was set up to compare the clinical outcomes of patients who underwent proton or state-of-the-art photon radiotherapy in the treatment of locally advanced oesophageal cancer. A total of 19 public and industry partners across Europe are participating in the 11 working groups. The project is funded by the Innovative Medicines Initiative, IBA and Varian.

The trial has been initiated in Denmark, Belgium and Switzerland, and more than 40 patients have been randomised. Additional centres in Italy, France and Germany are expected to start recruiting this year.

## Workshop reports

### Beyond Physical Dose: organised by WPs1, 5 & 6

Armin Lűhr, Damien Weber and Dirk Wagenaar

The aim of the workshop "Beyond physical dose" was to define a unified quantity beyond dose to describe the radiobiological effects of proton radiation in patients. This workshop was preceded by a survey of European proton therapy centres to identify areas in which consensus could be reached regarding the current and future use of parameters other than dose (e.g., linear energy transfer and RBE) in clinical facilities.

The workshop started with the presentation of the vision of seven institutes on this topic. This was followed by discussion sessions on the clinical use of physical parameters other than the dose (session A) and the use of biological parameters (session B). Finally, in session C, a summary of sessions A and B was presented, and consensus was reached on several statements on these topics. The next step is to form a task group to write a white paper that summarises the results of this meeting and the preceding survey.

### Evidence-based Proton Therapy: organised by WP1

Hans Langendijk

Task 1 was addressed in the workshop on evidence-based proton therapy. The general objective of this workshop was to establish a firm basis for evidence-based particle therapy on a European level.

Cai Grau presented an overview of ongoing clinical trials on particle therapy. In contrast with some years ago, when virtually all clinical trials on particle therapy were initiated in the USA, the number of registered clinical intervention trials in Europe increased to 31 in 2023. The importance of performing clinical trials was highlighted and discussed. A new development is the design of hybrid trials that combine classic randomised controlled trials (RCTs) and model-based clinical evaluation. This combination enables the validation of the model-based approach for testing new technologies that are aimed at reducing the occurrence of radiation-induced side effects.

Several ongoing clinical trials were discussed by David Thompson (proton beam radiotherapy for oropharyngeal cancer (TORPEDO) study), David Lines (proton beam therapy for breast cancer (PARABLE)), Jeppe Friborg (proton vs. photon therapy by the Danish head-and-neck cancer study group (DAHANCA 35)), and Alexander Valdman (proton vs. photon therapy in high-risk rectal

cancer(PRORECT)). The discussions highlighted the lessons learned from the experiences of the clinicians.

The most important reasons that patients give for not consenting to participation in clinical trials on proton therapy are: travelling distances and times, fractionation schedules (the shorter, the better), prolongations of waiting times and logistics around plan comparisons. Accrual can be improved through collaboration with other centres, patient involvement, national consensus on study procedures and improved logistics through the provision of accommodation, help with claiming travel costs, availability of dedicated nurses and improvement around plan comparisons.

A common feature of the ongoing trials was high compliance with the assessment of patient-reported outcome measures (80-90%), which was achieved by assigning a dedicated and very motivated team on a central or national level.

Hans Langendijk discussed the problems of performing RCTs to compare new radiation technologies. The generalisability of the results of RCTs can be hampered by rapid technological developments, differences in the technological features of both treatment planning and treatment delivery systems, and user-technology interplay. The model-based approach may tackle some of these problems. The impact of incremental technological developments, of dose to organs-at-risk and of the toxicity of new radiation technologies over time was nicely illustrated by Lisa van den Bosch. Hanna Rahbek Mortensen discussed the quality assurance programme of the PROTECT project and highlighted major differences in dose to organs-at-risk across participating centres, which illustrated the impact of technology-user interplay.

Marc Buyse presented the generalised pairwise comparisons (GPCs) of prioritised outcomes in the two-sample problem. GPC is a methodology that takes into account multiple primary endpoints in order to increase the statistical power of clinical trials and therefore to reduce the number of patients required. This is an attractive approach that is particularly suitable for the validation of the added value of rapidly developing technologies.

Lenny Verkooijen presented the trials within cohorts (TwiCs) approach. TwiCs use infrastructures (cohorts) to facilitate the conduct of multiple RCTs. TwiCs have been used to study interventions for cardiovascular diseases and multiple types of malignancies. The main advantages of TwiCs are: that they can be used as alternatives to pragmatic clinical trials with the current standard used as a comparator; they lead to more efficient patient accrual; they enrol patients who are more representative of the general population; they mean patient-centred informed consent; and they involve no or little contamination by or disappointment among patients. TwiCs are increasingly used worldwide and reports of them have been accepted by international peer-reviewed medical journals.

The next step for 2024 is to work on one or two white papers on trial methodologies to validate the added value of new radiation technologies such as particle therapy.

For Task 2, the content of the generic assessment, as well as the assessments for the central nervous system/ base of skull, head and neck, breast, oesophagus, lung and prostate have been completed. The content of the assessments for sarcoma and lymphoma remains to be determined. For 2024, the plan is to complete the latter two assessments and review the existing assessments in order to see whether modifications are required based on new insights and

developments. For the assessments of paediatric tumours, we decided to join the EU project on the health effects of cardiac fluoroscopy and modern radiotherapy in paediatrics (HARMONIC).

To establish the IT infrastructure, a new WP within EPTN has been created.

## Adaptive proton therapy workshop- organised by WPs 4 & 5

Aswin Hofmann, Alessandra Bolsi (WP4) and Christian Richter, Tony Lomax (WP5)

This was the first meeting of a new EPTN task group on adaptive proton therapy. It has been decided that this topic should be a cross-WP *task group*, rather than a new WP, and this meeting was organised to discuss how best to organise such a group. Two representatives of each EPTN WP were invited to participate, and there were 14 participants at the workshop from eight proton therapy institutes.

At the workshop, types of adaptive therapy were divided into 'categories' and 'timescales' by which any particular adaptive therapy approach could be described.

*Categories of adaption*

| | | |
|---|---|---|
| Up-front | : | Always adapt |
| Image-based | : | Based on expected dose changes due to acquired image changes |
| Dosimetry-based | : | Based on dose changes evaluated on acquired images |

*Timescales*

| | | |
|---|---|---|
| Off-line | : | Adapt in ≥ one day |
| Daily off-line | : | Image and adapt within one day |
| On-line | : | Image and adapt while patient on couch |
| Near real-time | : | Adapt in seconds, non-continuous beam |
| Real-time | : | Adapt in sub-seconds, continuous beam |

Given these definitions, a daily adapted approach may be described as, for instance, 'up-front, on-line' adaption, whereas a fully off-line approach based on dose recalculations may be described as 'dosimetry-based, off-line'.

The group believes that these definitions can help to avoid ambiguity when we talk about the many different approaches to adaption in the literature and during workshops/discussions.

Given the broad range of topics and dependencies of adaptive therapy, the task group will operate and coordinate across all existing WPs in the EPTN. As such, there are nine main aims, and the involved EPTN WPs have been initially defined for the task group:

| | |
|---|---|
| 1. Risk-benefit analysis | : All WPs |
| 2. Competences of disciplines and educational programme | : WPs 1, 3 |
| 3. Reporting standardisation | : WPs 1, 4, 5 |
| 4. Commissioning and quality assurance protocols | : WPs 2, 4, 5 |
| 5. Cost-efficiency / resources | : WP 7 |

6. Technical requirements : WPs 2, 4, 5

7. Trigger-level consensus : WP 1

8. Impact on margins (incl. robustness) : WPs 1, 2, 4, 5

9. Connection research and clinic : All WPs

This list is not seen as exhaustive and will be expanded as the task group develops. It is proposed that at least one member from each WP in the EPTN should report back on the activities of the adaptive therapy task group to their respective WP. However, the detailed structure and functioning of the task group should be defined in more detail by three coordinators who cover the main professions. The coordinators will be Pieter Populaire (Leuven), Francesca Albertini (PSI) and Rita Simoes (University College London Hospital).

## Concluding remarks

The EPTN has seen continued expansion and an ever-growing annual meeting, which indicates the importance of and continued interest in the network. It has been agreed that an additional WP on data registry should be established. The workshops saw high numbers of participants who discussed important and topical subjects. The success of the workshops as part of the EPTN annual meeting has made them integral to this yearly event.

We would like to thank everyone who contributes to the continued growth and work of the EPTN, and for a successful ninth annual meeting and workshops.

We hope for another productive year of the EPTN and continued active engagement from its members in the years to come.

See you all next year in Vienna autumn 2024!

**Damien Weber, Cai Grau, and Dietmar Georg**
Co-chairs of the EPTN

**Damien Weber,** Switzerland

**Cai Grau,** Denmark

**Dietmar Georg,** Austria