



RESEARCH PROJECTS

Reports from work packages (WP)

WP1: Clinical

(co-ordinator: Hans Langendijk, The Netherlands)

Prospective registry on proton therapy in Europe – results of survey and proposal

Vincent Gregoire, MD, PhD, Radiation Oncology Department, Centre Léon Bérard, Lyon, France;

Esther Troost, MD, PhD, Radiation Oncology Department, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; and

Damien Weber, MD, PhD, PSI, Villigen, Switzerland

Introduction

One of EPTN's work packages is centred around the gathering of clinical data in order to gain evidence on the status of proton therapy. In parallel with prospective controlled trials, prospective real-life data registries may provide important information on the outcome of patients treated with proton therapy, both in terms of efficacy (e.g., local control and survival) and safety (i.e. side effects and patient-rated outcome measures). Prospective data registrations offer a unique opportunity to find out which factors in the care process lead to the best results for patients. Identification of variations between centres and the sharing of results and best-practice care processes may offer major incentives to improve the quality of all proton-therapy centres, implement guidelines, and justify the opening of new centres across Europe.

Goal of the survey and methodology

In the context of the EPTN, the goal of the survey presented here was to investigate the willingness of the staff of major European proton-therapy centres to participate in the creation of such a prospective data registry. The responsible physicians and/or physicists at nine European proton-therapy centres were interviewed.

Summary of the main findings

The following statements could be drawn from the interviews.

- 1) All shareholders said that, in order to move the field forward, data had to be shared among European proton-therapy centres.
- 2) All shareholders agreed that a two-step move that involved the sharing of the so-called generic data first and then the in-depth, tumour-specific data subsequently (see Table 1) was a sensible way to go.
- 3) All shareholders agreed that an *ad-hoc* agreement should be put in place to define precisely who, when, how and for what purpose the data should be accessible and to identify a steering committee of the registry.
- 4) All shareholders insisted that data transfer between the local database and the European proton-therapy registry should be done automatically.
- 5) The format and the extent of the local database would be highly variable from centre to centre, from both the content and the format points of view.
- 6) Legal and ethical issues regarding data transfer among centres and countries were raised by all centres. These issues can be solved, but this will have to happen before any centralised database can be set up. In this respect, a distributed, learning-based registry has been proposed as an alternative to avoid data transfer among countries and databases.
- 7) It was reiterated by most centres that, at the time of the set-up of the registry, all European proton-therapy centres would be expected to be willing to join, providing that the same rules and governance would apply to them.

Conclusions of the survey

- It is clear that the selected European proton-therapy centres are willing to participate in the creation of a European database, with the proviso that adequate governance and agreements are put in place.
- Data will be collected in two steps: generic data first, followed by tumour-specific data. Data on tumour control and toxicity are scored in the latter phase.
- Even though EPTN is an ESTRO taskforce, ESTRO cannot fund the database. Negotiations with the European Organisation for the Research and Treatment of Cancer were unsuccessful. Therefore, we will strive to set up collaboration between academia and industry.

WP2: dose assessment, quality assurance, dummy runs, technology inventory

(co-ordinator: Oliver Jäkel)

Sairos Safai, Switzerland; Oliver Jäkel, Germany; Stefano Lorentini, Italy

As of October 2022, WP2 comprised 46 participants from 31 centres in 13 countries.

The fifth WP2 workshop was held online in February 2020. Besides organisational matters, a thematic workshop on the update of the International Atomic Energy Agency's (IAEA's) technical report series (TRS) 398 to be held in Aarhus, Denmark, was prepared. There were also progress reports from the subgroups on *absolute and reference dosimetry* (a presentation of current and future activities of the UK National Physical Laboratory in this field) and an update on the inventory for *dosimetry instrumentation*. A new subgroup was proposed, which would prepare *dosimetry guidelines for proton beam modelling*, based on input from Carles Gomà. This proposal was greatly appreciated and a detailed timeline for the preparation of the guidelines was discussed.

A third thematic workshop on the update of TRS 398 was held in a hybrid format in April in Aarhus, Denmark, organised by Liliana Stolarczyk and Ole Norevang. In this workshop, 42 people from 26 institutions participated, with the large majority being on-site. The workshop stretched over three days. It started with an on-site measurement campaign during the afternoon of day one, the aim of which was to compare the monitor calibration in different centres. An interesting finding was the difference in energy dependence, which was found to be significant even among machines from the same vendor. This will be analysed further and followed up in order to understand the reason for these differences, which point towards some differences in the monitoring systems.

Over the next 1.5 days, the different aspects and status of the update of TRS 398 were discussed. Unfortunately, the IAEA has still not published the report, even though the full report was reviewed in the summer of 2021.

Another initiative, which was started very recently by Liliana Stolarczyk of the Danish Center for Particle Therapy (DCPT) with working group 9 of the European Radiation Dosimetry Group, is investigating the ways in which linear energy transfer (LET) in particle beams can be measured. Such measurements may be required if LET-based optimisation is used in treatment planning systems (TPSSs), and adequate validation of LET distributions may be requested. The initiative will start with a comparison of different techniques and detectors that can be used to determine LET during a measurement campaign at the DCPT, which will be held before the end of 2022.

For the next (fourth) thematic workshop, in 2023, it was suggested that we apply to hold an ESTRO physics workshop on patient-specific quality assurance. WP2 and WP5 would organise this workshop jointly, and a proposal will be submitted to ESTRO in January 2023.

The yearly meeting of WP2 on updates regarding current activities and organisational aspects will be held online in December 2022.

WP3: education

(co-ordinator: Morten Høyer, Denmark)

The WP3 group, with representation of radiation therapists (RTTs), MPs and research officers from European particle centres (28 participants from 15 institutions) gathered for a meeting on 7 May 2022 during ESTRO2022 in Copenhagen to discuss future educational activities in particle therapy.

Workshops that would be supplementary to the ESTRO School teaching course in particle therapy and other teaching courses were discussed. The first workshop was cancelled twice due to COVID-19, but a workshop with a focus on proton therapy for brain and skull-base tumours has now been held (13-14 October 2022 at the -PSI). The workshop had 28 participants and faculty from the PSI and abroad. It was a great success thanks to a dedicated faculty and a very enthusiastic audience. Future workshops will be modified based on the experience gained from this pilot event. At the Copenhagen meeting, participants highlighted a need for parallel sessions for RTTs and additional workshops that would focus on specific themes rather than on specific tumour types. This



will be introduced in future workshops. The EPTN 2022 meeting in Leuven discussed the idea that workshops could be based on themes suggested by other EPTN WPs and could utilise members of these WPs as workshop faculty.

It was decided in Copenhagen that the WP3 group would meet once per year during the ESTRO congress and that there would be an additional virtual meeting during the autumn to discuss educational strategies within particle therapy in Europe. A virtual WP3 meeting is planned for November.

WP4: image guidance in particle therapy

(co-ordinator: Markus Stock, Austria)

Aswin Hoffmann, Alessandra Bolsi, Markus Stock

Image guidance for particle therapy (IGPT) is essential to guarantee accurate dose delivery and to minimise the effects of range uncertainties that are related to patient set-up uncertainties and anatomical changes that occur during the course of therapy. Multiple imaging modalities for IGPT are available and used routinely in clinics. However, due to a lack of standardised procedures for IGPT, most centres have developed their own strategies, which are based on each centre's particular infrastructure, technical implementation and dose delivery strategy.

The first aim of WP4 was to gain insight into the current clinical practice parameters of IGPT in European particle-therapy centres. Therefore, multiple detailed surveys for specific localisations, classified as abdomen, prostate, brain, breast, craniospinal irradiation and extremities, have been sent out in the past few years. Response data has been collected and analysed by the respective body-site-specific sub-working groups, with the aim to identify common procedures, their limitations and potential improvements. These results describe the current clinical practice of IGPT in Europe and will be submitted for publication before the end of 2022.

An IGPT research project has been initiated. It is a multicentre evaluation of the inter- and intrafraction accuracy of patient positioning for brain-tumour patients who undergo particle therapy. The study aims and endpoints are currently being defined within the WP. A pilot phase in collaboration with a few pre-selected centres has been completed successfully, and a call for the inclusion of all centres will be launched in Q1 2023. Centres that have interests in IGPT will receive a project description, which will clarify the details of the project, its aim and a specific template. The template will have to be set up ad-hoc to facilitate and harmonise the collection of IGPT data for brain-tumour patients.

After a long interruption in in-person meetings due to the COVID-19 pandemic, we are organising the fifth annual workshop, which will take place on-site at MedAustron in Wiener Neustadt (Austria) on 17-18 November 2022. A call to participate in this meeting has already been sent out by the ESTRO office to all centres that have an interest in WP4.

WP5: treatment planning systems in particle therapy

(co-ordinator: Edmond Sterpin, Belgium), Tony Lomax and Christian Richter

TPSs are essential for the performance of accurate and effective particle therapy, and are an important part of the particle therapy workflow. In this WP, our aim is to review and provide recommendations on numerous aspects of the treatment planning process.

The work was initially divided into six main tasks for consideration:

- collective TPS specifications;
- planning standards and case solutions (with the collaborative network of several European particle therapy centres known as IPACS);
- TPS commissioning and validation;
- alternatives to patient-specific verifications;
- computed tomography/Hounsfield unit (CT/HU) calibration; and
- analysis of robustness.

Two new ones have now been added:

- 4D planning, and
- the role of LET.

Collective TPS specifications

These have been defined and have been published on the ESTRO website, and vendors contacted for their input. The WP5 group, however, believes that the current specifications in this fast-moving area should be reviewed, and we are looking for volunteers to do this.



Planning standards and case solutions

This is a task that is being undertaken in collaboration with the IPACS group, which has done most of the work already. Planning comparisons for a head-and-neck case have been performed within the IPACS group, and the results have now been published (Stock et al., *Acta Oncol.* 2019; 12: 1720-1730). The next case (a skull-base chordoma) is being prepared.

In addition, and with the infrastructure in proton international research (INSPIRE) project, a blind treatment planning study is being organised by the University of Groningen and PSI. A case has been prepared, and all EPTN proton therapy centres have been contacted to see if they will participate. At the time of writing, 14 centres have responded positively and the case will be distributed to all soon.

Alternatives to patient-specific verifications

After the success of the workshop that was held at PSI in 2019, a joint meeting has been organised between WP5 and WP2 (dosimetry), as there is clear overlap in this topic. A Zoom meeting was held between the leaders of WP2 and WP5 on 31 August to discuss this collaboration. At this meeting, it was decided that a 1.5-day workshop on patient-specific quality assurance for proton therapy would be proposed for inclusion at the ESTRO physics workshop in 2023. The deadline to submit a proposal to ESTRO is January 2023, and a follow-up meeting between WP2 and WP5 leaders will be organised in November/December to work on this proposal.

CT/HU calibration

Robustness analysis

The plan to perform a multi-centred robustness analysis based on a single patient has currently been paused. Instead, a robustness “consensus” initiative is being prepared, which will follow the workflow of the advisory committee for radiation oncology practice (now the ESTRO guidelines committee). In addition, two systematic reviews are being prepared on robust optimisation and robustness evaluation; a first draft of the latter has been produced.

4D planning

This group has been heavily involved in an update to the patterns of practice for adaptive and real-time particle therapy initiatives. The work has been presented at several conferences, and two papers based on it are about to be submitted. A round-table discussion took place in Delft in November 2021 and a 4D optimisation review paper has been published¹. An abstract on the same topic was presented at the particle therapy cooperative group meeting this year (PTCOG 2022). A review/guideline paper on 4D dose evaluation methodologies, in collaboration with the PTCOG thoracic subcommittee, is being prepared, as well as a ‘vision’ paper on the future of 4D particle treatments.

The role of LET

This group first met in June 2021, when the main aims of the group were defined (see WP5 reports from 2021), and the role of LET in treatment planning was a main topic for the general WP5 meeting on 18 October 2022. In addition, a meeting between WP6 (radiation biology) and WP5 leaders took place on this topic on 7 October. A follow-up meeting between WP6 and WP5, with the aim of arriving at a consensus proposal regarding the role of LET in treatment planning, will be organised before the end of the year.

Next steps for WP5

As has been discussed previously, we would like more involvement of clinicians and RTTs/dosimetrists in this WP and are happy to consider having a medical doctor as co-chair of the WP or as co-task leader in specific tasks. For RTTs/treatment planners, a specific task could be considered, which would be led and organised by RTTs/treatment planners. In addition, a few new potential topics for this WP have been discussed. We believe that a task on adaptive therapy is urgently needed, but that this involves many different EPTN working groups (clinical, imaging, TPS, dosimetry etc). The idea of defining a specific ‘adaptive’ working group will be discussed with the EPTN general committee. Other potential tasks that have been discussed are single-dose ultra-high dose rate (FLASH) and arc proton therapy. However, we believe that it is currently too early to set up dedicated tasks in these areas. These topics will be reviewed at subsequent meetings.



Reference:

1. Knopf, A.C., Czerska, K., Fracchiolla, F., Graeff, C., Molinelli, S., Rinaldi, I., Rucincki, A., Sterpin, E., Stützer, K., Trnkova, P., Zhang, Y., Chang, J.Y., Giap, H., Liu, W., Schild, S.E., Simone, C.B., Lomax, A.J., 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 Feb 18;S0167-8140(22)00102-5. doi: 10.1016/j.radonc.2022.02.018.

WP6: radiobiology and relative biological effectiveness

(co-ordinator: Amin Lühr, Denmark)

Background

Protons have a differential biological effect compared with photon irradiation. Part of this is accounted for in the concept of relative biological effectiveness (RBE). The RBE is known to be variable for all ions, and therefore for protons; the RBE of protons increases with LET and inversely with dose per fraction. The current use of an RBE of 1.1 for protons is the subject of a longstanding debate. This discussion has been intensified by recent clinical data, which suggests that there is a relationship between an increased biologically effective dose, i.e. an increased RBE, and the occurrence of clinically relevant adverse effects. Three central questions in the ongoing discussion regarding clinical RBE are:

- is the variability of the proton RBE of clinical relevance?;
- is it necessary actively to consider the variability of RBE in proton treatment?; and
- if so, what measures would be suitable to counteract RBE uncertainty safely?

Survey – current clinical practice regarding RBE in European particle therapy centres

In an online survey conducted by WP6, all 25 European proton centres from 14 European countries were asked to reply to 38 questions dealing with the research question: is RBE variability taken into account in clinical practice at their institution?

Remarkably, all 25 centres responded and showed great interest in the RBE topic. The main findings, which were published as an article [1], included :

- all centres follow current guidelines and prescribe a constant RBE of 1.1;
- all centres are aware of the variability of proton RBE;
- all centres perform at least some measures to counter the uncertainty from RBE; and
- most of the centres were open to considering variable RBE in the future and urged standardisation of RBE solutions to ensure exchangeability of clinical data between centres.

Collaboration topic: towards a roadmap on handling variable RBE in the clinic

Based on our earlier workshops, the dedicated RBE survey and several discussions, we could identify a general feeling of uncertainty regarding a variable RBE among proton therapy centres. The current problem, however, is that no strategy on how to consider variable RBE in clinical routine is readily available or generally accepted. It is important to understand that opinions on handling variable RBE vary markedly. This may add uncertainty and inconsistency to patient treatment.

Therefore, it is the goal of WP6 actively to support the development of an EPTN-wide roadmap on handling variable RBE in the clinic. This proposal received strong support from participants at the EPTN 2022 meeting in Leuven. To achieve this, it is essential to bring together relevant partners and their interdisciplinary knowledge, e.g., from other EPTN WPs. Dedicated meetings to discuss mutual interests and to draw attention to each other's activities in this respect have so far been held with WP1 and WP5.

The next step will be to hold a multidisciplinary EPTN workshop dedicated to RBE in 2023. The aim will be to define an EPTN roadmap on variable RBE and to harmonise reporting and handling of variable RBE.

Development of WP6 structure

As another step forward, some further development of the WP6 structure is currently being discussed. While WP6 has so far considered itself as one unified group that handles all radiobiology topics, it seems useful to split WP6 into task groups, each of which considers a main subject. The topics of these groups have yet to be specified and agreed.



WP7: health economy

There is no report from this WP.

EPTN WP coordinators

	Title	Coordinators
1	Clinical	Hans Langendijk (Groningen, The Netherlands): leader Roberto Orecchia (Milan, Italy) Karin Haustermans (Leuven, Belgium) Daniel Zips (Berlin, Germany) Jacques Balosso (Grenoble, France) Esther Troost (Dresden, Germany)
2	Dose assessment, quality assurance, dummy runs, technology inventory	Oliver Jäkel (Heidelberg, Germany) Sairos Safai (Villigen, Switzerland) Stefano Lorentini (Trento, Italy)
3	Education	Morten Høyer (Aarhus, Denmark) Marco Schwarz (Seattle, USA)
4	IGPT	Aswin Hoffmann (Dresden, Germany) Alessandra Bolsi (Villigen, Switzerland)
5	TPS in particle therapy	Christian Richter (Dresden, Germany) Tony Lomax (Villigen, Switzerland)
6	Radiobiology, RBE	Manjit Dosanjh (Geneva, Switzerland) Bleddyn Jones (Oxford, UK) Armin Lühr (Dortmund, Germany) Jörg Pawelke (Dresden, Germany) Martin Pruschy (Zurich, Switzerland) Brita S. Sørensen (Aarhus, Denmark)
7	Health economy	Yolande Lievens (Ghent, Belgium)

Collaborative EU projects

Proton versus photon therapy in the treatment of oesophageal cancer (PROTECT) ***(C. Grau, Denmark)***

PROTECT compares the clinical outcomes of proton therapy and state-of-the-art photon radiotherapy in the treatment of locally advanced oesophageal cancer.

A total of 19 public and industry partners across Europe have joined forces in this ambitious collaborative clinical research project to set new standards for the clinical use of proton radiotherapy.

The project is funded by the innovative medicines initiative, the European Federation of Pharmaceutical Industries and Associations, and the companies Ion Beam Applications and Varian, part of Siemens Healthineers. It is the first public-private partnership in which funding from the industry has been matched by funding from the EU.

The project, which comprises 11 working groups, is expected to take six years. The first three patients have been recruited in Denmark.

Real-time adaptive particle therapy of cancer (RAPTOR) ***(S. Korreman, Denmark)***

RAPTOR is an EU horizon 2020-funded programme. The principal investigator is Francesca Albertini. The project brings together 13 beneficiaries and 15 partner organisations. The aim of RAPTOR is to train early-stage researchers in the field of medical physics with a focus on real-time adaptive particle therapy.



The project began in March 2021 and will end in February 2025.

The first meeting of the RAPTOR school took place virtually on 13-17 December 2021 and was attended by 95 participants. The second meeting occurred from 4 to 7 September 2022 in Ljubljana, Slovenia, and the third meeting is planned to take place over the period 10-15 September 2023 in Ascona, Switzerland.

Ongoing clinical trials

A search of ClinicalTrials.gov has shown that, as of October 2022, there are 19 phase II and nine phase III European proton clinical intervention trials that are recruiting participants. An overview of these trials was presented at the workshop.

Some emerging proton interventional studies were also mentioned: one by the Danish lung cancer group into heterogeneously hypofractionated radiotherapy for locally advanced non-small-cell lung cancer, which is at the randomised phase II stage, and the PROTIS study by Cancer Research UK into sinonasal cancer (randomised phase III stage).

The network members were invited to communicate to the EPTN coordinators any other trials that they were aware of.

EPTN session at PTCOG 61

PTCOG 61 is taking place on 12-17 June 2023 in Madrid, Spain. ESTRO has a memorandum of understanding in place with the EPTN, which foresees educational sessions at events of the Society. A joint session is being planned for PTCOG 61.

Concluding remarks

The question was raised as to whether the preference was to have the EPTN meeting in 2023 as a live, blended, or virtual event. Various proposals were made and based on the discussion the organizers have decided to hold a **live meeting in October 2023 as a two-day event**, with WP meetings taking place either before or after the plenary meeting. The dates will be communicated shortly.

The question was also raised as to whether the current WPs should be re-defined. Many members were interested, e.g., those on some sub-groups of the WPs. This gave rise to the idea that a sub-group should not necessarily be linked to a WP but to cross-fertilise where possible. This request will be discussed between the EPTN coordinators and the WP-leaders.

The meeting ended with a short visit to the PARTICLE centre.

See you all at the next annual workshop of EPTN in 2023.

