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Short communication

Proton therapy and the European Particle Therapy Network: The past, present and future[☆]



Protonthérapie et le réseau européen de thérapie par particules : le passé, présent et futur

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ARTICLE INFO

Article history:

Received 15 May 2020

Received in revised form 19 May 2020

Accepted 20 May 2020

Keywords:

Proton therapy

EPTN

European research networks

Cancer

European research infrastructure

Mots clés :

Protonthérapie

EPTN

Réseaux de recherche clinique européens

Cancer

Infrastructures de recherche européennes

ABSTRACT

Proton therapy is delivered to selected cancer patients presenting with rare tumours, for which a dose escalation paradigm and/or a reduced dose-bath to the organs at risk is pursued. It is a costly treatment with an additional cost factor of 2–3 when compared to photon radiotherapy. Notwithstanding the 180'000 patients treated with protons, scarce robust clinical evidence is available to justify the administration of this treatment modality. The European Particle Therapy Network (EPTN) was created in 2015 to answer the critical European needs for cooperation among protons and carbon ions centres in the framework of clinical research networks. EPTN with other European groups will launch a number of prospective clinical trials that could be practice changing if positive. Alternative way to generate clinical data could be provided by alternative methodologies, such as the Dutch model-based approach, or could be provided by European infrastructure projects.

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RÉSUMÉ

La protonthérapie est délivrée pour des patients cancéreux sélectionnés atteints en général d'une forme rare de tumeur pour laquelle une stratégie thérapeutique d'augmentation de dose et/ou réduction de l'irradiation des structures critique radiosensibles est indiquée, avec un coût additionnel entre 2 et 3 par rapport à la radiothérapie par photons. Malgré le fait que 180 000 patients aient reçus un traitement par protons, il n'existe que peu d'évidence clinique pouvant justifier l'administration d'un tel traitement. Le réseau européen de thérapie par particules (*European Particle Therapy Network* : EPTN) a été créé en 2015 afin de répondre aux besoins européens de coopération parmi les centres de proton/ion carbone thérapie dans le cadre de réseaux de recherche clinique. L'EPTN, avec d'autres groupes européens, lancera un certain nombre d'essais cliniques prospectifs qui pourraient modifier la pratique s'ils s'avèrent positifs. D'autres moyens de générer des données cliniques pourraient être fournis par des méthodologies alternatives, telles que l'approche basée sur le modèle néerlandais, ou pourraient être fournis par des projets d'infrastructure européens.

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[☆] Presentation at the 2020 SFRO meeting in Paris, October 8th 2020.

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1. Introduction

Proton therapy uses positively charged particles, namely protons, rather than photons to treat cancer. This radiation modality can be used alone or in combination of X-ray radiotherapy (RT) for a number of tumours, not limited but including central nervous system primary tumours, sarcoma or bone cancers. The position of the Bragg peak within the tumour volume permits the planner to paint optimally the dose deposition to the target. Numerous dose-comparative plannings have shown an increase in dose conformity for protons when compared to photons, especially in the low-dose bath, too well known to merit a repeat citation here. At high-energy, it can treat deep-seated tumours with a substantial decrease of the integral dose delivered to the patient when compared to radiotherapy, by a factor of approximately 2 to 5 [1]. Although many papers will state in their introduction section that proton therapy is a new treatment modality in the therapeutic armamentarium, it is not. The idea of using protons in cancer management was first suggested in 1946 by physicist Robert R. Wilson in his seminal paper published on that year [2]. The first attempts to use proton therapy to treat patients began in the 1950s in mainly nuclear physics research facilities, such as the Lawrence Berkley National Laboratory in the US [3], or in the Svedberg Laboratory/University of Uppsala in Sweden. The delivery of protons was however, limited to few areas of the body, as these early proton therapy delivery systems involved horizontal beams only. In the late 1970s, imaging advancements coupled with the development of computers for treatment planning systems and improved treatment delivery technology made proton therapy clinically accessible for selected cancer patients in some certain centres. In 1976, a first patient was treated for a pelvic rhabdomyosarcoma at the Harvard Laboratory Cyclotron in Boston that was only decommissioned in 2001 after many years of successful radiation treatments for cancer patients. In 1991, another time-mark was achieved when Loma Linda Medical Center administered its first proton treatment in a hospital based-facility. Many hospital-based proton therapy centres followed suit in Asia, the US and recently Europe [4]. In 2018, it was estimated that approximately 180,000 patients were treated with protons (<https://ptcog.ch/index.php/patient-statistics>). Unfortunately, this large number of patients did not generate high-level of clinical evidence (mainly level 3–5; Oxford Centre for Evidence-Based Medicine; <http://www.cebm.net/index.aspx?o=5653>) that could justify this costly treatment in unselected cancer patients.

2. Costly treatment

The additional cost factors of proton therapy in respect to radiotherapy is approximately two to three [5], but varies from countries to countries, depending on insurance/national reimbursement policies. These treatment related costs will add some financial burden to the overall cancer management related costs and productivity losses, which has increased substantially this last decade to approximately 16 to 20 billion euros nationally in 2009 in the UK, France and Italy individually (<https://canceratlas.cancer.org/taking-action/economic-burden/>). The productivity loss due to premature death secondary to cancer can reach up to 0.5% of the gross domestic product (GDP) and has increased in low-income countries. Proton therapy could potentially reduce late adverse radiation-induced events, improve HR-QOL, and/or improve patient's outcome reducing thus the overall economic impact of cancer in adults and children alike [6]. As financial resources are scarce, it is of paramount importance to consider the cost-effectiveness of proton therapy. Many cost-effectiveness studies using the Markov model, have been undertaken with conflicting results [7–11]. Proton therapy may

be cost-effective for the management of brain tumours in children. More economic analyses involving not only mathematical models are however urgently needed to evaluate the benefit of proton therapy for non-central nervous system paediatric tumour management and for adults with cancer.

3. Lack of data

There are several reasons why, after several decades of clinical use of proton therapy for cancer management, no high-level clinical evidence was generated. First and foremost, proton therapy was delivered in non-clinical environments, mostly nuclear research facilities or physics' laboratories. Individual physicians, who could not bring fully the clinical trials ecosystem, inexistent at former times, and medical philosophy in these research Physics' facilities, referred patients with no incentive other to provide a therapeutic alternative strategy for a challenging cancer patient. Medical team were usually embryonic, and funding was usually lacking to organized patient's follow-up appropriately. Patient's and tumour characteristics were not prospectively captured at the time of treatment and the retrospective analyses of data could only generate low-levels of clinical evidences. Second, patients treated with protons were managed with several delivery modality, treatment paradigms (pre- vs. postoperative proton therapy, radical proton therapy) and fractionation schemes with no national or international strategy to come with unified treatment protocols. The series stemming from these cohorts were consequentially usually retrospective in nature with the well know bias associated with these type of analyses. Third, much debate has been generated on the ethical implication of a phase III randomized trial randomizing selected cancer patients to either protons or photons, the main concern being the lack of equipoise for the photon arm [12,13]. Non-ethical issues complexing the activation of a randomized trial with protons, includes but is not limited to the applicability of results in the general population and the characteristics of patients treated with protons in fee-for service systems that may significantly differ to those presented by photon patients, have been summarized in a recent paper advocating the model-based approach [14].

4. The European Particle Therapy Network (EPTN)

The development of proton therapy has increased substantially in the early 2000s, mainly in the US and in Asia. In Europe, the development has been much slower, but within the last decade, more than 20 clinical facilities have opened with a consequential better access to this treatment modality for European cancer patients [15]. Early on, several European academic radiation oncologists identified the aforementioned lack of clinical evidence for proton therapy highly problematic. It was felt that proton therapy was too much of a therapeutic niche and should be fully embedded into the broader European radiotherapy community. Additionally, it was also discussed that the existing national and international European networks, such as the European Organization for the Research and Treatment (EORTC), should be used to generate clinical evidence and high-quality data that could better define the indications for proton therapy [16]. To this end, the European particle Therapy Network (EPTN; www.estro.org/Science/Activities/EPTN) was created in 2015 and a first annual meeting was organized in 2016 in Brussels. Shortly after in 2017, it became officially a taskforce of the European Society for Radiotherapy (ESTRO). That same year, EPTN took the decision to associate its clinical research for selected holistic research programs with the EORTC, which has a regulatory expertise and has a record of accomplishment of independence and accountability in clinical research. Once such example is the ParticleCARE initiative (EORTC 18033;

Table 1
Prospective European randomized trials comparing protons to photons irradiation for cancer treatment.

Trial	Type of cancer	Year of activation	Model-based approach enriched population	Randomisation ratio ^a	Number of patients (accruing target)
DAHANCA 35	Head and neck squamous cell carcinoma	2020	Yes	2/1	500
TORPEdo	Oropharyngeal squamous cell carcinoma	2020	No	2/1	180
IMPERATOR	Head and neck squamous cell carcinoma	Unknown	Yes	1/1	350
PROTECT	Squamous cell carcinoma/adenocarcinoma oesophagus	2021	No	1/1	440
DBCG trial	Breast	2020	No ^b	1/1	1500

DBCG: Danish Breast Cancer Group Proton; DAHANCA: Danish Head and Neck Cancer group.

^a Proton/photon

^b Enrichment without using a model-based approach

www.estro.org/Science/Activities/E2RADIATE) that belongs to the E²RADIaTE portfolio that serves as an umbrella for multiple cohort studies that will prospectively collect real world data to support radiotherapy research. This strategy was recently validated by the EORTC strategy meeting on radiotherapy [17]. The overall aim of EPTN is thus to answer the critical need to cooperate among protons and carbon ions centres in the framework of clinical research networks. It has currently seven work packages, detailed in a recent publication [18], led by a number of medical physicists, radiation oncologists and radiobiologists. Of note, this European strategy of tackling the lack of evidence issue in a timely manner was later discussed at the European level on November 2018 at the European Commission in Luxembourg, thus validating the earlier endeavor in 2015. The non-permanent commission on proton therapy embedded in the Directorate General for Health and Food Safety concluded at that time that key challenges and knowledge gaps regarding this treatment modality should be addressed urgently and that international collaboration was of outmost importance in providing critical evidence for protons. It was decided that the European Investment Bank was going to commission a study that should have been discussed in Q2 2020 but was rescheduled to a later date due to the coronavirus disease 2019 (covid-19) situation. The members of EPTN have discussed and conceptualized a number of prospective trials that will be detailed in the following section [19].

5. The model-based approach

In the Netherlands, the so-called model-based approach is utilized for proton therapy patient selection. The model-based approach can be applied for selection of patients for proton therapy but also for the clinical validation of the added value of protons when protons are used to with the aim to reduce radiation-induced side effects [14,20]. Model-based selection is based on the assumption that protons can only have a clinical benefit in terms of prevention of radiation-induced side effects if the dose to relevant organs at risk can be reduced as compared to the best photon technique (Δ Dose) and that this dose reduction is expected to result in a clinically relevant reduction of the risk of side-effects (i.e. Δ NTCP). To this purpose, an in-silico planning comparison study is performed in each individual patient to assess Δ Dose. Then the expected benefit (Δ NTCP) can be estimated by using Normal Tissue Complication Probability (NTCP) models. The ultimate selection is based on predefined Δ NTCP-thresholds, e.g. the Δ NTCP for grade 2 or higher side effects should be at least 10%.

Model-based clinical evaluation is an evidence-based method that can be used as an alternative for randomized controlled

trials. In model-based clinical evaluation, the observed toxicity rates after in patients selected for proton therapy according to the model-based approach are compared to the expected NTCP-values based on the photon plan from the in-silico planning comparison study. As such, each patient serves as its own control [14].

6. Current prospective randomized trials in Europe

There are currently several prospective trials on the European drawing board (Table 1). For head and neck cancers, three trials will be launched or are currently accruing patients. The Danish group is actively recruiting patients with advanced head and neck squamous cell carcinoma in a multicentre phase III trial (DAHANCA 35) comparing protons to photons. Objective assessment of swallowing and salivary flow as well as acute/late toxicity and quality of life will be undertaken. Of note, this group will use a hyperfractionated accelerated regimen combined with nimorazole, as in the previous DAHANCA study [21]. This trial is currently in its pilot phase. The TORPEdo trial will assess the potential radiation-induced toxicity reduction as a result of the delivery of protons using a conventionally fractionated regimen (Table 1) [22]. It is the first proton therapy trial from the UK and will randomized intensity-modulated proton- vs. photon therapy (with a 2/1 ratio) for oropharyngeal squamous cell carcinomas, regardless of the human papilloma virus (HPV) infection status. With an accrual target of 180 patients, concomitant chemoradiotherapy and bilateral lymph node irradiation will be administered to study patients. A strong translational program is foreseen and samples will be collected to assess the opportunity of bio-marker driven trial in the not too distant future. Importantly, the trial was conceptualized with the secondary aim to validate the NTCP photon and proton models derived from the model-based approach in use for patient selection in the Netherlands [20,23]. The third and last advanced stage (III/IV) head and neck squamous cell carcinoma trial proposal is the IMPERATOR trial from the EORTC. Definitive radiotherapy or concurrent chemoradiotherapy delivered with curative intent is allowed. Total toxicity score will be the primary endpoint, a composite endpoint for swallowing and salivary dysfunction. The ambitious aim of this trial is to validate the model-based approach by selecting patients who would most likely derive clinically relevant benefits from particle therapy in terms of prevention of radiation-induced side effects. Δ NTCP-profile will be computed for all patients and if a predefined threshold of the Δ NTCP-profile will not be met, the patients will be treated with photons (photon IMRT by selection) if the country will choose to use the model-based approach paradigm for patient selection. For these countries, patients are treated with protons when the

predefined threshold of the Δ NTCP-profile is met (proton therapy by selection). In countries in which the model-based selection is not used, patients are eligible for random allocation to either protons or photons intensity-modulated irradiation, provided that the predefined threshold of the Δ NTCP-profile is met (photon therapy at random and proton therapy at random). This design will not only enable to compare protons to photons but also to compare photon/protons at selection vs. random. The design of this important trial will possibly be revised due to budgetary issues but plan is to use the model-based approach for the selection of patients with head and neck squamous cell carcinoma.

For squamous cell carcinoma or adenocarcinoma newly diagnosed oesophageal cancer, the Danish group has taken the lead in the design of a trimodality treatment comparing intensity-modulated radiotherapy/volumetric archtherapy to intensity-modulated proton therapy (PROTECT trial; Table 1). Two dose levels are allowed, namely 41.4 Gy in 23 fractions and 50.4 Gy in 28 fractions. As in the TORPEDO trial, tissue and blood samples will be collected to enable future translational research. Primary endpoint will be the rate of pulmonary complications at 6 months measured by Common Toxicity Criteria for Adverse Events (CTCAE) v5.0, grade 2 or higher, by the Esophageal Complications Consensus Group (ECCG) and the Comprehensive Complication Index (CCI).

Finally, the Danish Breast Cancer Group Proton will embark in a phase III randomised trial with an accrual target of 1500 (Table 1). The aim is to demonstrate reduced cardiac morbidity for patients treated with protons who need to be treated with locoregional nodal irradiation. It is based on dose-planning study showing that for patients where the dose-volume constraints to the heart and lungs cannot be met without compromising the target dose, a proton plan was always superior [24]. A patient will be a candidate if mean heart dose is at least 4 Gy or V17/20 lung is at least 37%, no need for comparative treatment planning. It is estimated that 7% of all breast radiotherapy patients will be candidates (20% of the patients who were offered locoregional radiotherapy). Endpoints are radiation associated ischaemic and valvular heart disease at 10 years after radiotherapy.

7. European infrastructure project

Evidence in the field of proton therapy can also be generated outside a prospective randomized trial as discussed earlier. The infrastructure in Proton International Research INSPIRE (www.protoninspire.eu) will generate such evidence, led by the Manchester group, is an infrastructure pan-European project involving 17 participating European institutions, that aims to provide a world-leading integrating activity for European research in proton therapy. This 5-million euros project will facilitate transnational access to proton therapy research beamlines, exchange of knowledge and best research practice across and between proton therapy centres throughout Europe and developing an innovation pipeline allowing research to be translated into clinical practice and industrial products. This program is organised in 11 work packages, including but not limited to training, radiobiology, mathematical modelling and communication/dissemination.

8. Conclusions

As identified by the Directorate General of the European Community, there is a dire need to mitigate the knowledge gaps in proton therapy and better define the indications for cancer patients of this radiation modality. The EPTN has created research-networking opportunities and has enabled to embed proton therapy in the overall radiation oncology community. Several

prospective randomized trials will be activated in Europe for head and neck and oesophageal cancer that will provide the health professionals and lay people high-level of clinical evidence for these two cancers.

Disclosure of interest

The authors declare that they have no competing interest.

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