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Overview of research and therapy facilities for radiobiological experimental work in particle therapy. Report from the European Particle Therapy Network radiobiology group

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ABSTRACT

Particle therapy (PT) as cancer treatment, using protons or heavier ions, can provide a more favorable dose distribution compared to X-rays. While the physical characteristics of particle radiation have been the aim of intense research, less focus has been placed on the actual biological responses arising from particle irradiation.

One of the biggest challenges for proton radiobiology is the RBE, with an increasing concern that the clinically-applied generic RBE-value of 1.1 is an approximation, as RBE is a complex quantity, depending on both biological and physical parameters, such as dose, LET, cellular and tissue radiobiological characteristics, as well as the endpoints being studied. Most of the available RBE data derive from in vitro experiments, with very limited in vivo data available, especially in late-reacting tissues, which provide the main constraints and influence the quality of life endpoints in radiotherapy. There is a need for systematic, large-scale studies to thoroughly establish the biology of particle radiation in a number of different experimental models in order to refine biophysical mathematical models that can potentially be used to guide PT.

The overall objective of the European Particle Therapy Network (EPTN) WP6 is to form a network of research and therapy facilities in order to coordinate and standardize the radiobiological experiments, to obtain more accurate predictive parameters than in the past. Coordinated research is required in order to obtain the most appropriate experimental data. The aim in this paper is to describe the available radiobiology infrastructure of the centers involved in EPTN WP6.

Introduction

While the physical characteristics of particle radiation have been the aim of considerable research, less focus has been placed on the actual biological responses resulting from particle irradiation (i.e. protons and heavier ions). There is still a range of unresolved radiobiological questions that need to be addressed in order to fully exploit the advantages of particle radiation for radiotherapy.

Relative biological effectiveness (RBE) is a practical quantitative concept, which has been introduced to account for an increased efficiency of protons and other particles relative to conventional radiotherapy. This higher efficiency is due to an increased linear energy transfer (LET), a measure of the quality of different types of radiation [1]. RBE is defined as the ratio of a dose from conventional photons to a dose from any other particle to produce the same biological effect. This is complicated by the fact that RBE is not a constant, but depends, among others, on the specific tissue, on the particle energy, on the study endpoint and on the fractional dose [2]. The complicated factors which influence RBE were recently the topic of an Expert Workshop in Dresden, and the different aspects are thoroughly covered in a paper, with the overall conclusion that more data are needed in order to fully enlighten the potential impact of the RBE [17]. Experimental RBE data for determining clinical relevant RBE values are of great importance, but it should also be emphasized that the biological effects of particle radiation do not necessarily apply to all endpoints that rely on a dose response effect that can be corrected with a RBE factor. Emerging data are rather suggesting a different biology [3–5],

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which in terms of high level clinical outcomes may remain essential.

To be able to comply with the issues of a different radiobiology and a varying RBE in particle therapy, it is crucial to have experimental biological studies to determine the extent and magnitude of these effects. This should include both hypothesis generating in vitro experiments, as well as the necessary next-step, in vivo studies, which will enable simulation of clinical treatments in animal models, especially of the late tissue vascular and fibrotic complications which are very important in radiotherapy. Until very recently only acute reacting tissues have been subjected to RBE estimations. Likewise for the tumor, experimental in vitro data emerge and indicate that the genetic background of the tumor also influences the RBE [6,7]. High quality preclinical research is necessary to secure the continuous foundation for clinical research.

In principle, tumor RBE values are obtainable from clinical data provided the analytical methods used are correct. Equations containing RBEmax and RBEmin values, each linked to LET, as well as time-dependent repopulation corrections, may be required for data sets that contain different time-dose-fractionation schedules. Similar considerations apply to normal tissue RBE estimations, although additional care must be taken about dose-volume relationships, which may also influence outcomes [8].

To fully utilize the benefits of particle therapy, a concerted research effort is called for to provide systematic radiobiological experiments for the development of biological models and implementation of these in treatment planning systems for particle therapy. The aim of the European Particle Therapy Network (EPTN) Work Package 6 (WP6) is to form a network of research and therapy facilities. This would open for the possibility of standardizing radiobiological experiments, and coordinate the research in order to deliver the needed experimental data.

Explore basic principles in particle radiobiology

The radiobiological response to particle radiation is potentially different from that of photon radiation on many levels, as demonstrated in a number of experimental studies. This was highlighted in a recent special issue of Frontiers in Oncology [9]. There is a continuing need for both the precise quantitative characterization of these differences, as well as the exploration of the detailed molecular mechanisms of the cellular response to different types of radiation. This is necessary for further optimization of the therapeutic use of particle radiation and the potential integration of biological aspects into treatment planning.

To fully exploit the advantages of particle therapy, there is a range of unresolved radiobiological questions that need to be answered, where examples of key objectives include investigation of the differential cellular responses to different radiation qualities. There is also a need to establish the interaction of chemotherapeutic agents and other biological modifiers of radiation on the effect of radiotherapy. Furthermore, the current available in vitro data should be supplemented with a coherent dataset of basic radiobiological measurements taken under homogeneous conditions.

An overview of centers currently active in particle radiobiology research – The questionnaires

In view of the marked heterogeneity of equipment, beam energies, beam qualities and the important reference sources of radiation (which can influence the magnitude of RBE values obtained in experimental studies), as well as the main topics of research mentioned, there is a clear need for coordination of the overall research objectives, with achievement of defined goals in specific centers according to their expertise. Such an approach is more likely to produce useful data for the clinic in a reasonable time and at the lowest cost. The evolution of our present knowledge has depended on a very fragmented non-harmonized approach, in different centers using different experimental systems and beam parameters, which has demonstrated many important phenomena, but which will need increasing quantification to obtain the most accurate values of the key parameters that influence selected biological effects.

Attempts to establish an international laboratory for in vitro studies at CERN working in collaboration with clinical and animal experimental centers elsewhere [10,11] appear not to be proceeding according to the original plan supported by the radiation oncology community. Equally disappointing was the decision by the EC not to support radiation related research in the Horizon 2020 funding round. In these circumstances, there is an even greater need to achieve a planned collaborative approach for future research in this important area, beginning with experimental in vitro and in vitro studies that are highly relevant to clinical needs.

To obtain an overview of the current activities within radiobiology research in particle radiation in European institutions, a questionnaire was sent to all centers that had ongoing and/or future plans for particle therapy. The questionnaire contained questions on physics, dosimetry and the quality controls, as well as availability of reference radiation. The planned or current experimental biology work was also highlighted.

Of the participating centers, all 13 have, or will have, proton beam available, while 5 centers will have carbon ion beams available, and/or access to other ions, or other ions are projected to be available. Of the 5 centers with multiple ions available, four have the possibility of rapid switching between ion species, within an assigned experimental time-slot. A list of the participating centers can be seen in Table 1.

The energies available for protons range from 62 to 252 MeV in most centers, with GSI having the possibility of using low energy, in 5–15 MeV/u range or high energy, in 80–1000 MeV/u range. With regard to beam, all 13 centers have scanned beams, while 4 of the centers also have passively scattered beam available.

The information on the physical properties is summarized in Table 1.

The types of biological experiments planned at the different facilities vary greatly, but include both basic radiobiology, and more specialized studies. Ten centers have, or will have, a dedicated experimental beam room. For the biological experiments, most of the centers have access to a clinical photon beam, either on-site or nearby, for reference radiation for comparative experiments.

The information on the experimental conditions is summarized in Table 2.

The specific need for RBE in vivo studies

Overall, in particle therapy there is a surprising lack of data from recent in vivo experiments, which in other treatment modalities has been regarded as a necessary link between the more hypothesis generating in vitro experiments to patient treatment. As a necessary next-step from in vitro studies, in vivo studies enable simulation of clinical treatments in animal models. Cell experiments give good indications of the various effects, but in vivo there are a complexity of biological functions playing together, which is impossible to reproduce in vitro. Therefore, experiments in animal models give a much more precise picture of the actual effect. However, data from in vivo models may take years to develop.

At present, one of the crucial points in particle radiobiology is to establish the RBE of different normal tissues in a systematic, large-scale in vivo setup, using relevant particles. This should include

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