Radiotherapy and Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Review

# "Radiobiology of Proton Therapy": Results of an international expert workshop

Armin Lühr [a,b,c,1], Cläre von Neubeck [b,c,1], Jörg Pawelke [a,b], Annekatrin Seidlitz [b,c,d], Claudia Peitzsch [b,c,e], Søren M. Bentzen [f], Thomas Bortfeld [g], Jürgen Debus [h,i,j], Eric Deutsch [k,l], Johannes A. Langendijk [m], Jay S. Loeffler [n,o], Radhe Mohan [p], Michael Scholz [q], Brita S. Sørensen [r], Damien C. Weber [s], Michael Baumann [a,b,c,d,e,h,2,*], Mechthild Krause [a,b,c,d,e,2], for the expert workshop"Radiobiology of Proton Therapy"

[a] *Helmholtz-Zentrum Dresden – Rossendorf, Institute of Radiooncology – OncoRay;* [b] *OncoRay – National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden – Rossendorf;* [c] *German Cancer Consortium (DKTK), Partner Site Dresden and German Cancer Research Center (DKFZ), Heidelberg;* [d] *Department of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden;* [e] *National Center for Tumor Diseases (NCT), Partner Site Dresden, Germany: German Cancer Research Center (DKFZ), Heidelberg, Germany; Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany, and; Helmholtz Association/Helmholtz-Zentrum Dresden – Rossendorf (HZDR), Germany;* [f] *Division of Biostatistics and Bioinformatics, Department of Epidemiology and Public Health and the Maryland Proton Therapy Center, Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore;* [g] *Physics Division, Department of Radiation Oncology, Massachusetts General Hospital, Boston, USA;* [h] *German Cancer Research Center (DKFZ), Heidelberg;* [i] *Department of Radiation Oncology, University Heidelberg German Consortium for Translational Oncology (DKTK);* [j] *National Center for Tumor Diseases (NCT), Heidelberg, Germany;* [k] *Department of Radiation Oncology Gustave Roussy Cancer Campus, INSERM, 1030 Villejuif;* [l] *Université Paris-Sud, Faculté de Medecine du Kremlin Bicetre Paris Sud, Le Kremlin-Bicêtre, France;* [m] *Department of Radiation Oncology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands;* [n] *Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston;* [o] *Department of Neurosurgery, Massachusetts General Hospital and Harvard Medical School;* [p] *Department of Radiation Physics, UT MD Anderson Cancer Center, Houston;* [q] *GSI Helmholtz Center for Heavy Ion Research, Department of Biophysics, Darmstadt, Germany;* [r] *Dept. Experimental Clinical Oncology, Aarhus University Hospital, Denmark;* [s] *Center for Proton Therapy, Paul Scherrer Institute, ETH Domain, Villigen, Switzerland*

ARTICLE INFO

*Article history:*
Received 29 March 2018
Received in revised form 17 May 2018
Accepted 17 May 2018
Available online xxxx

*Keywords:*
Relative biological effectiveness (RBE)
Proton beam therapy
Radiobiology
Treatment planning
Trial design

ABSTRACT

The physical properties of proton beams offer the potential to reduce toxicity in tumor-adjacent normal tissues. Toward this end, the number of proton radiotherapy facilities has steeply increased over the last 10–15 years to currently around 70 operational centers worldwide. However, taking full advantage of the opportunities offered by proton radiation for clinical radiotherapy requires a better understanding of the radiobiological effects of protons alone or combined with drugs or immunotherapy on normal tissues and tumors. This report summarizes the main results of the international expert workshop "Radiobiology of Proton Therapy" that was held in November 2016 in Dresden.

It addresses the major topics (1) relative biological effectiveness (RBE) in proton beam therapy, (2) interaction of proton radiobiology with radiation physics in current treatment planning, (3) biological effects in proton therapy combined with systemic treatments, and (4) testing biological effects of protons in clinical trials.

Finally, important research avenues for improvement of proton radiotherapy based on radiobiological knowledge are identified. The clinical distribution of radiobiological effectiveness of protons alone or in combination with systemic chemo- or immunotherapies as well as patient stratification based on biomarker expressions are key to reach the full potential of proton beam therapy. Dedicated preclinical experiments, innovative clinical trial designs, and large high-quality data repositories will be most important to achieve this goal.



## Introduction

While the use of proton beam radiation therapy for cancer started more than 60 years ago, the number of proton radiotherapy facilities has steeply increased over the last 10–15 years to currently around 70 operational centers worldwide. The physical

* Corresponding author at: German Cancer Research Center (DKFZ), Heidelberg, Germany.
*E-mail address:* michael.baumann@dkfz.de (M. Baumann).
[1] Share first authorship.
[2] Share last authorship.

https://doi.org/10.1016/j.radonc.2018.05.018
0167-8140/

properties of proton beams, that are a focused delivery of radiation at the Bragg peak, with very steep decline of the radiation dose behind the target volume, offer the possibility potentially to reduce toxicity by reducing the dose to adjacent normal tissues. However, biological effects of proton therapy, in particular the potential impact of their increased effectiveness, are much less well understood than those of photons. This is partly due to a limited number of proton centers that have a dedicated and well-equipped experimental area to perform the necessary preclinical experiments, but also due to a lack of systematic collection of high-quality experimental data. Worldwide more than 150,000 patients have been treated with protons, but there is still a lack of high-quality outcomes data for this radiation modality. Taking full advantage of the opportunities offered by proton radiation for clinical radiotherapy requires a better understanding of the radiobiological effects of protons alone or combined with drugs or immunotherapy on normal tissues and tumors. In order to define the current status of knowledge and evidence and to derive the most important open questions for proton radiobiology research for the coming years, an international expert workshop "Radiobiology of Proton Therapy" was held in November 2016 in Dresden. Workshop participants are listed under "Acknowledgements". This report summarizes the main results of this workshop.

## RBE dependence and experimental RBE data

### *Physical properties of proton irradiation*

The clinical use of proton beams is motivated by higher dose conformity to the target volume compared to conventional radiation and consequently their potential for dose reduction in normal tissue and therapy with high-energy photon beams [1–6]. Protons moving through tissue are slowed down and lose energy mainly by a large number of Coulomb interactions with the atomic electrons and a much smaller number of nuclear interactions, resulting in energy (dose) deposition in the tissue along the proton path. The loss of energy per unit path length, i.e., the linear energy transfer (LET), depends on the velocity of the proton and increases with penetration depth: initially, over a longer distance, it increases slowly and then, toward the end of the proton track, rapidly. Accordingly, proton beams deposit relatively low doses in the entrance channel in front of a tumor and most of their energy over a well-defined narrow region near the end of range of Bragg peak. The position of the Bragg peak varies as a function of the initial beam energy, allowing for placing the dose maximum inside the target volume. In clinical applications, the target volume substantially exceeds the width of the Bragg peak of mono-energetic proton beams. Several beams of different energies are superimposed either by passive scattering or active beam scanning techniques to deliver the prescribed dose throughout the entire target volume in depth producing a spread-out Bragg peak (SOBP) [7]. As a result, the dose in the distal part of the SOBP is deposited by a relatively larger portion of lower energy and, therefore, higher LET protons (Fig. 1), while the dose in the proximal part is deposited mostly by protons that have a higher energy and thus lower LET [8]. Also, the distribution of LET along the penetration path of a clinical proton beam varies with the widths and position of the SOBP in the patient. For intensity-modulated proton therapy, it is intended that the combined dose distributions from all beams are homogeneous in the target while the dose and LET distributions per beam in the target volume may be highly heterogeneous.

### *Relative biological effectiveness of protons*

Apart from total absorbed dose, the radiation-induced biological response depends on various physical and biological parameters such as radiation type, dose rate, dose fractionation, dose distribution, cell and tissue type, microenvironment including oxygenation level, and the biological endpoint [9]. Current clinical experience in radiotherapy almost completely relies on data from high-energy photon therapy. In order to account for a higher effectiveness of proton beams as compared to conventional photon therapy, the relative biological effectiveness (RBE) is used. By definition, the RBE is given as the ratio of doses of a reference relative to a test irradiation, respectively, producing the same biological radiation effect. Current clinical practice, recommended by the International Commission on Radiation Units and Measurements (ICRU) [10], uses a constant RBE value of 1.1 for proton therapy in all tissues and across the entire irradiated volume, irrespective of the dose and LET. This consensus value is based on measured *in vivo* RBE data (mostly from the 1970s) at the center of the SOBP. However, a number of have investigations demonstrated variable RBE values in different test systems. This observation challenges the use of a single approximate RBE value for protons in clinical practice.

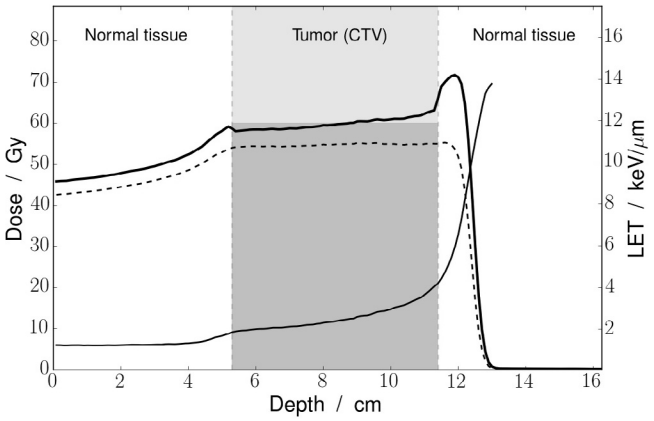


**Fig. 1.** Physical dose (dashed line) and dose-averaged linear energy transfer (LET) (solid line) for a clinical proton treatment field that considers physical uncertainty margins. The effective biological dose (bold line) was calculated by multiplying the physical dose with experimental dose- and LET-dependent *in vitro* RBE data [89] for tumor and normal cells within the tumor and the normal tissue, respectively.

### *Variation of RBE – available data*

A large amount of data is available (see, e.g., the reviews by [9,11]) showing large variations and considerable uncertainties in proton RBE values. RBE values for clonogenic cell survival *in vitro* indicate a substantial spread between different cell lines. In general, RBE increases with increasing LET. An increase in LET, as observed for protons along the beam path, does not occur in photon therapy, where the LET is essentially constant. Hence, proton irradiation is more biologically effective than high-energy photons.

RBE averaged over a large number of cell lines increases with increasing dose-averaged LET and thus with depth in a typical SOBP from about 1.1 in the entrance region, to about 1.15 in the center of the SOBP, about 1.35 at the distal edge and about 1.7 in the distal dose fall-off region [11]. Furthermore, there is a trend toward increasing RBE as the $\alpha/\beta$ ratio (a parameter of the linear quadratic model inversely related to fractionation sensitivity of a biological endpoint) decreases. Moreover, *in vitro* data show an increase in RBE as dose per fraction is lowered [12,13]. There is a great need for *in vivo* experiments on normal tissues and tumors under well-defined conditions to define *in vivo* RBE values but also to unravel molecular mechanisms of radiobiological efficacy of proton beams. RBE data for clinical endpoints are presently too sparse to allow recommendations of RBE values in specific clinical

Please cite this article in press as: Lühr A et al. "Radiobiology of Proton Therapy": Results of an international expert workshop. Radiother Oncol (2018), https://doi.org/10.1016/j.radonc.2018.05.018